A Guide to Physiology & Bio-Chemistry

Reflex

MCQ & COLOUR ATLAS

Bangladesh is my Pride

14th Edition

Dr. Reza
Dr. Arzu
Dr. Ranzu

Following New Curriculum

14th edition

A Guide to Physiology and Bio-chemistry

Reflex

MCQ & Colour Atlas

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Publisher
Rehana Pervin (Shilpi)

Editor
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Tel : 0189430027; E-mail : ranzu14yahoo.net

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Editions

Fourteen Edition	:	10 April 2006
Thirteen Edition	:	21 February 2005
First Edition	:	May 1989

Available at :

Hafiz Book Centre	:	Govt. New Market, Dhaka, Phone : 507912
Parash Publisher	:	Govt. New Market, Dhaka, Phone : 863416
Sonia Medical Book House	:	24, Islamia market; Nilkhet, Dhaka, M : 019320710
Capital Books	:	116, 135 Islamia market; Nilkhet, Dhaka, M : 019320731
Bengal Library	:	117, Islamia market; Nilkhet, Dhaka, M : 0171134012
Pabna Book House	:	Islamia market; Nilkhet, Dhaka
Apex Book House	:	Islamia market; Nilkhet, Dhaka
Mukti Book House	:	119/20, Islamia market; Nilkhet, Dhaka
Elahi Medical Books	:	2, Hazrat Shahjalal market; Nilkhet, Dhaka
Bangladesh Medical	:	Islamia market; Nilkhet, Dhaka
Shamima Medical Books	:	134-135, Islamia market; Nilkhet, Dhaka
Luna Book International	:	Islamia market; Nilkhet, Dhaka
City Book House	:	125/26, Islamia market; Nilkhet, Dhaka
Dhaka Grantha Bitan	:	130, Islamia market; Nilkhet, Dhaka
Naogaon Book Emporium	:	129, Islamia market; Nilkhet, Dhaka

For all correspondence : **Little Publications**
House # : 91/G, Road # 7/A
Dhanmondi R/A. Tel : 9134876 (cell : 0189430027)

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Preface

It is well known that the students of medical scinces are greatly handicapped to the want of a concise and comprehensive text book on the subject as a whole. A beginner has therefore, no other way than to go through a number of voluminous text books on each one of the various branches of medical sciences and in doing so, he/she is very often confused about how much he/she should read and know. This confusion obviously leads to undue wastage of time and energy on the part of the student. Reflex, a promising guide to *Physiology & Bio-Chemistry*, which thought about this problem & was published in May 1989. Since its publication in 1989, Reflex has garnered cosiderable response from medical students & doctors.

In this 14th edition I have tried my best to give the reference of different authorized books e.g '*Text Book of Medical Physiology* 11th edition' by Arthur C. Guyton, M.D & Hall; '*Review of Medical Physiology*- 22th edition by William F. Ganong, MD; MD Samson wright's; MD Harold A. Harper; Davidson's Medicine; Robbins Pathologic Basis of Disease; in addition to some necessary diagrams & sketches with question's answer following the new curriculum so that the student will not have to face any problem in their study, together with their both written examinaion & viva voice.

All the chapters have been revised thoroughly, added some new figure & sketches, some new aspects on the basis of the latest edited "Physiology text books" mentioned above specially- '*Text Book of Medical Physiology- 11th edition*' by Arthur C. Guyton, M.D & Hall, and '*Review of Medical Physiology- 22th edition* by William F. Ganong, MD. All the systems are rearranged.

Multiple choice questions are added with their answers which will aid the students & doctors in particular content.

Color Atlas of physiology is added for medical students who want to master large amounts of information in a limited amount of time and review specific topics quickly & easily.

In this fourteen edition, MCQ portion is shifted from paper I and paper II to the Reflex, and paper I (written-SAQ), paper II (written-SAQ), and viva & practical (SOE, OSPE, & practical) is rearranged into one book named "***Reflex- Written & Viva*** (SAQ, SOE, OSPE & practical).

Efforts will be worthwhile if students find the work helpful in introducing this to the realm of the *vast science of medicine*. Please go through the text books.

With best wishes to all-

Dr. Md. Mustafizur Rahman Ranzu
10 April 2006

Dedicated
To
Our Beloved Parents



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Given under my hand and seal on this 29TH day of JUNE A.D. 2008.

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New curriculum

Notable features of new curriculum

1. M.B.B.S course will be of 05 (Five) years duration plus 01 (one) year Internship training.
2. There will be 3 professional Examinations during the M.B.B.S course :
   - i. At the end of 1 & 1/2 years : 1st professional.
   - ii. At the end of 3 & 1/2 years : 2nd professional.
   - iii. At the end of 5 years : Final professional.
3. There will be 2 (two) professional examination in one year.
   - i. In 1st week of January
   - ii. In 1st week of July

Subjects with marks allocated for different professional examination will be as follows :

i. ***In 1st Professional*** :

1. Anatomy	:	500 Marks
2. Physiology	:	400 Marks
3. Biochemistry	:	400 Marks
Total		*= 1300 Marks*

ii. ***In 2nd professional*** :

1. Pathology (300) + Microbiology (300)	:	600 Marks
2. Community Medicine	:	300 Marks
3. Pharmacology & Therapeutics	:	300 Marks
4. Forensic medicine & toxicology	:	300 Marks
Total		*= 1500 Marks*

iii. ***In Final Professional*** :

1. Medicine	:	500 Marks
2. Surgery	:	500 Marks
3. Obs. & Gynae	:	500 Marks
Total		*= 1500 Marks*

* Pass Mark will be 60% in each written, Oral, & Practical/Clinical Exam, Separately.

* Marks and pattern of questions in written examination in each subject will be as follows -

1. 10% Marks of written examination of each paper of each subject is allocated for formative assessment.
2. 20% Marks are allocated for MCQ for each paper. There will be separate Answer script for MCQ examination. Time allocation is 1 (one) minute for each question consisting of 5 stems (20 questions).
3. 70% Marks are allocated for SAQ (Except in Community medicine) for each paper.

* For oral, clinical & practical the examination system & Marks distribution is shown against each subject (See the Curriculum).

* Oral part of the examination will be structured oral.

* ***In Medicine*** : There will be 2 boards consisting of 4 examiners for oral, clinical & practical examination.

Board - I	:	1 examiner from Internal Medicine
	:	1 examiner from pediatrics
Board - II	:	1 examiner from Internal Medicine
	:	1 examiner from sub specialities (e.g. dermatology/Psychiatry)

There will be No Temp-Chart, slides and specimen in the Practical Examination.

* ***In Surgery*** : Oral, Practical & clinical examination will be held in Two separate days.

One Day	:	General Surgery
Another day	:	Ophthalmology + ENT

Assessment of Physiology

Summative Assessment (First Professional Examination)

Components	*Marks*	*Total Marks*
i. *Formative assessment :*	10+10	20
ii. *Written Examination :*		
Paper -I :		
a. MCQ	20	
b. SAQ	70	
Paper - II :		180
a. MCQ	20	
b. SAQ	70	
iii. *Practical Examination :*		
a. OSPE	40	
b. Traditional practical methods and experiments	50	100
c. Practical Note Book	10	
iv. *Oral Examination (Structured) :*		
a. 2 boards (4 examiners) : I. 2 internals II. 2 externals		100
Grand Total :		***= 400***

Paper I :

1. General Physiology
2. Blood
3. Cardiovascular
4. Respiratory System
5. Alimentary System.

Paper II :

1. Renal Physiology & body fluid
2. Endocrine & reproductive
3. Nervous System & Temp. Regulation
4. Special senses.

There will be separate Answer Script for MCQ & SAQ
Pass marks 60% in each of theoretical oral and practical.

1. **General physiology** :

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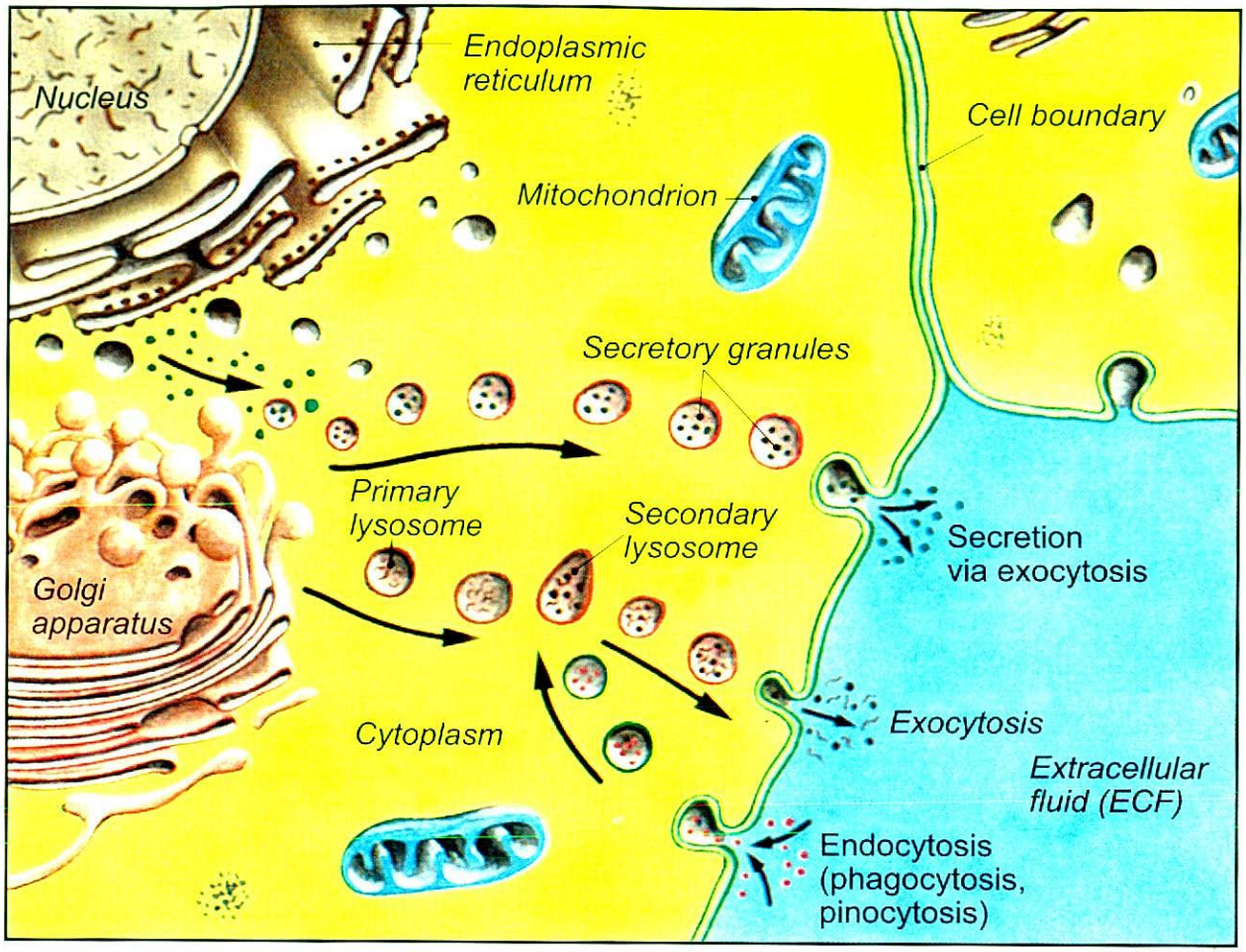
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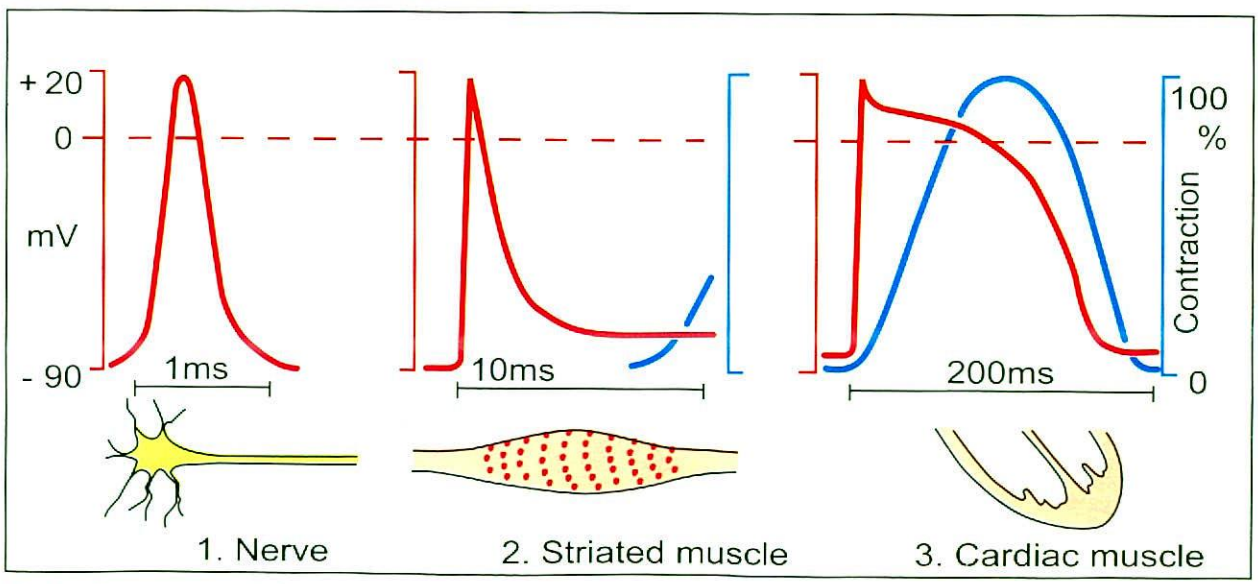
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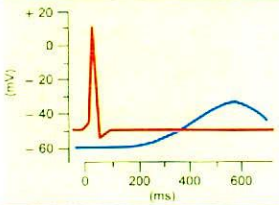
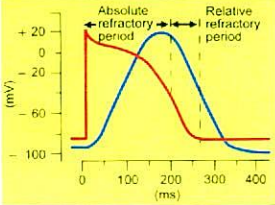
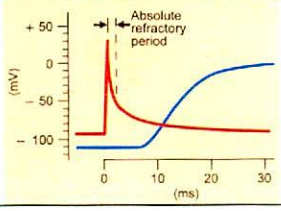


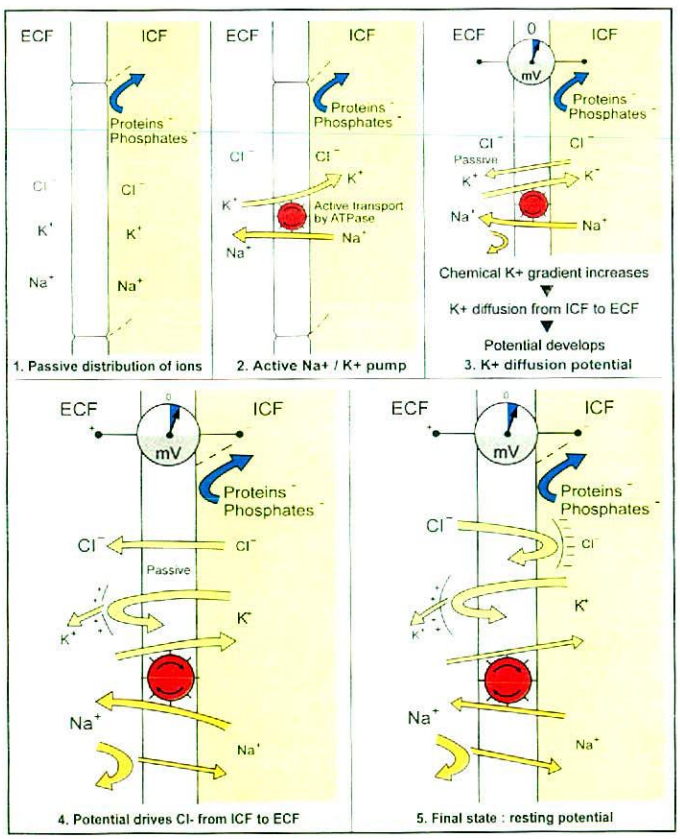
A. The cell. Endocytosis and exocytosis



B. Action potential - nerve and muscle

A. Structure and function of 3 classes of muscle

		Smooth muscle	Cardiac muscle	Skeletal muscle
				
Structure	Motor end-plate	None	None	Yes
	Fiber	Fusiform, short (max 0.4mm)	Branched	Cylindrical, long (max. 15 cm)
	Mitochondria	Few	Many	Few
	Nucleus/fiber	1:1	1:1	Several per fiber
	Sarcomere	None	Yes-max. length 2.6 µm	Yes-max. length 3.65 µm
	Syncytium	Yes (bridges)	Yes (functional)	No
	Sarcoplasmic reticulum	Poorly developed	Well developed	Extensively developed
	ATPase	Little	Average	Much
Function	Pacemaker	Yes (slow)	Yes (fast)	No (requirees neural impulse)
	Response	Graded	All or none	Graded
	Tetanus	Yes	No	Yes
	Operating range	Variabl length-tension curve	On rising portion of length-tension curve	On peak of length-tension curve
Response	Potential —— Mechanical tension ——			

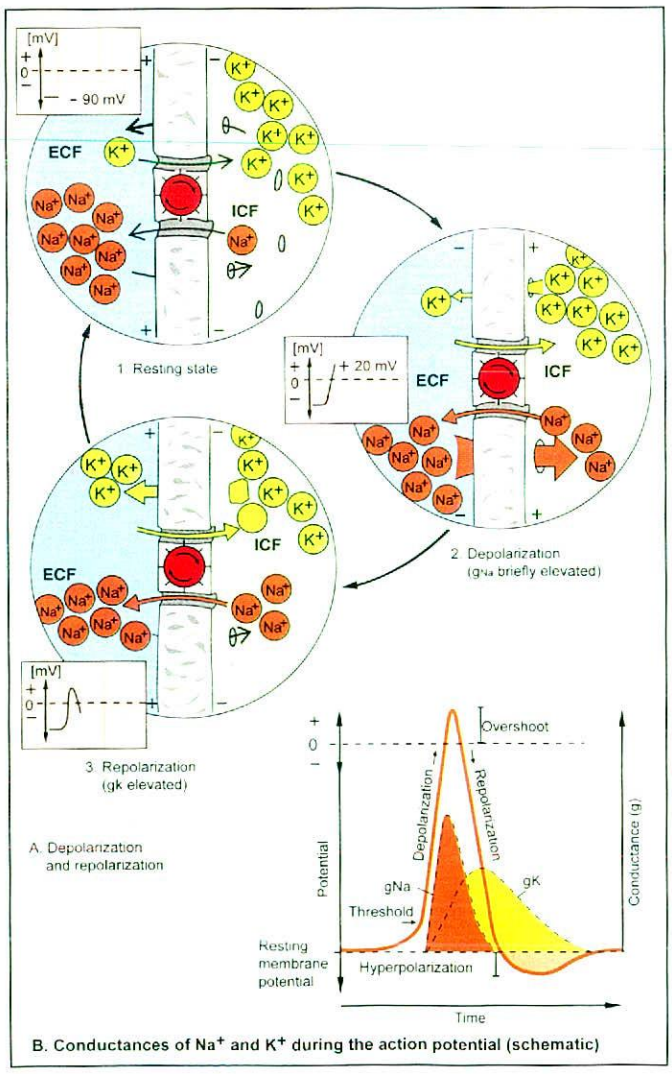


A. Causes and consequences of the resting potential

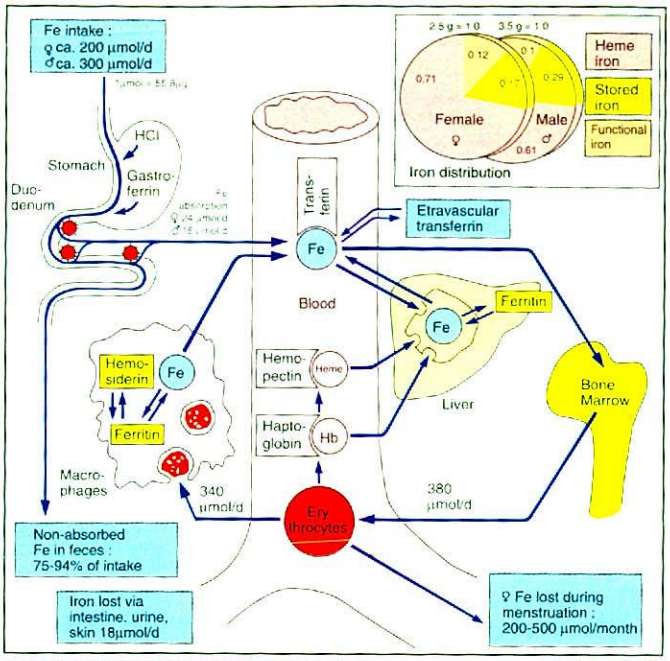
	"Effective" concentration (mmol/kg H_2O)		Equilibrium potential
	Interstitium (ECF)	Cell (ICF)	
K^+	4.5	160	- 95 mV
Na^+	144	7	+ 80 mV
H^+	$4 \cdot 10^{-5}$ (pH 7.4)	10^{-4} (pH 7.0)	- 24 mV
Cl^-	114	7	- 80 mV
HCO_3^-	28	10	- 27 mV

B. Typical "effective" concentrations and equilibrium potentials of important ions in skeletal muscle (37°C)

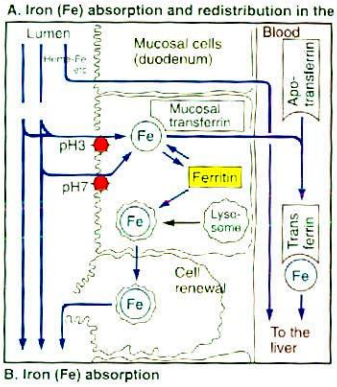
(after Conway)



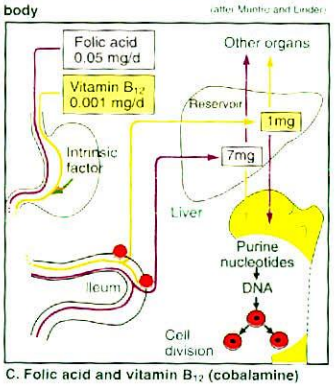
B. Conductances of Na^+ and K^+ during the action potential (schematic)



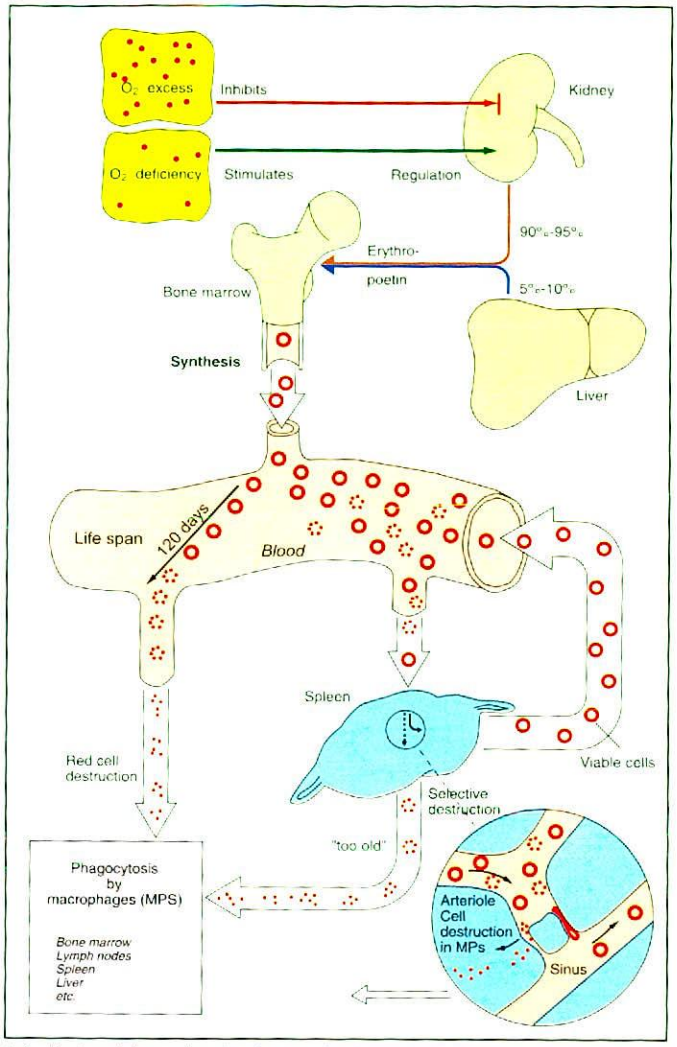
A. Iron (Fe) absorption and redistribution in the body



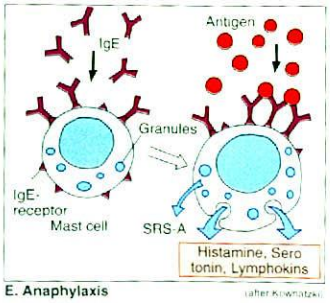
B. Iron (Fe) absorption



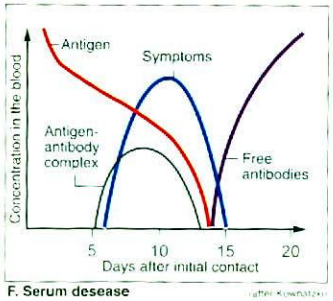
C. Folic acid and vitamin B_{12} (cobalamine)



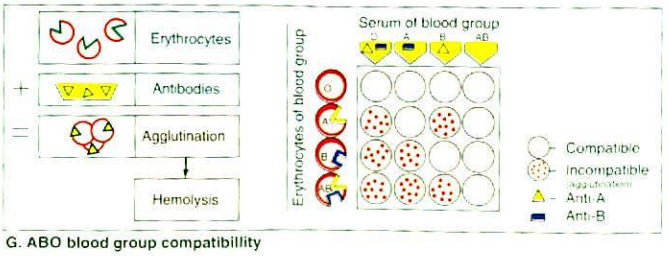
A. Synthesis and destruction of erythrocytes in adults



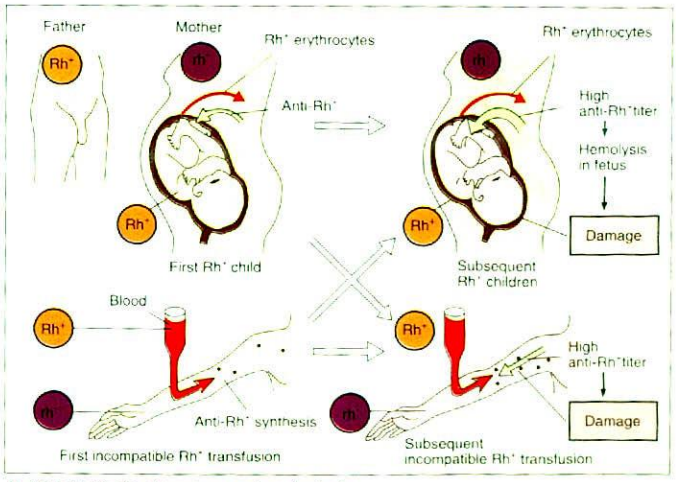
E. Anaphylaxis



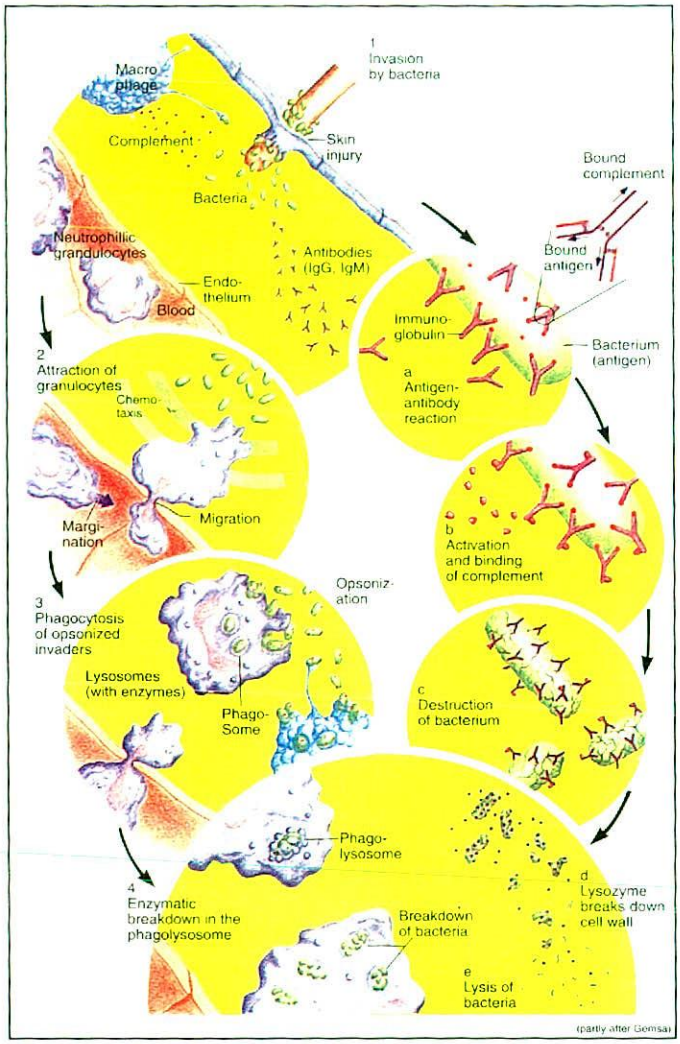
F. Serum desease



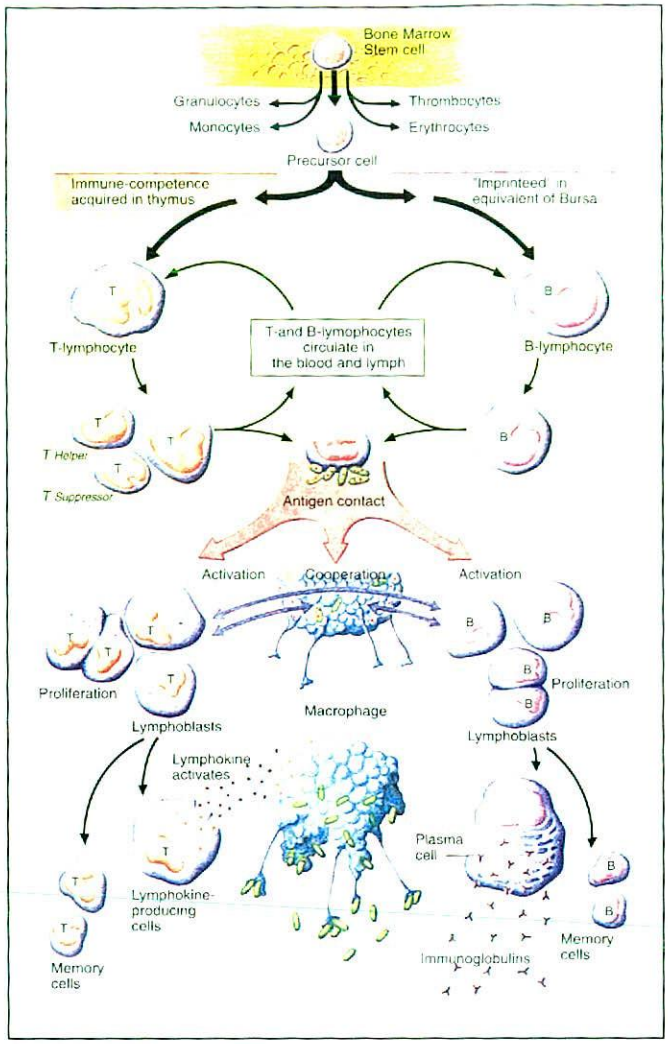
G. ABO blood group compatibillity



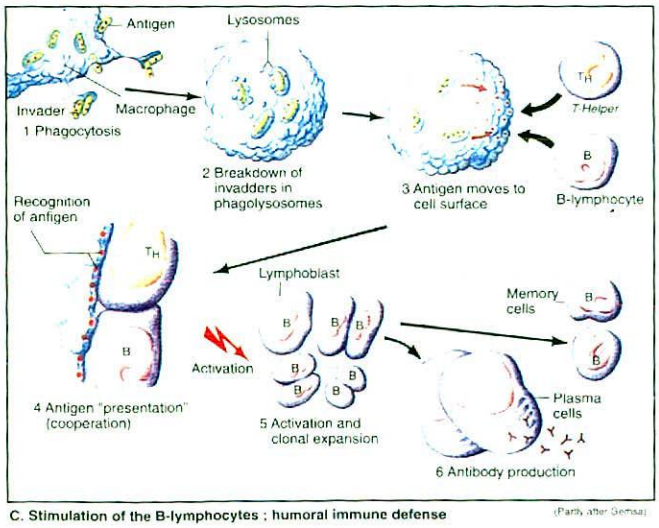
H. Rh sensitization (pregancy or transfusion)



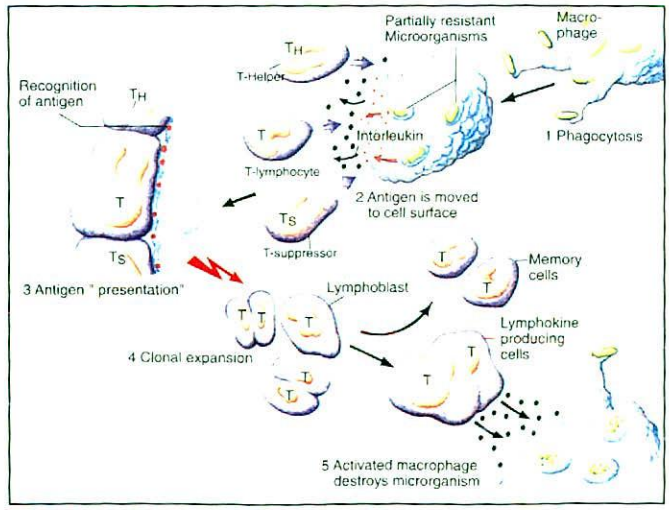
A. Mechanisms involved in defense against bacteria : phagocytosis (1-4) : extracellular lysis (1, a-e)



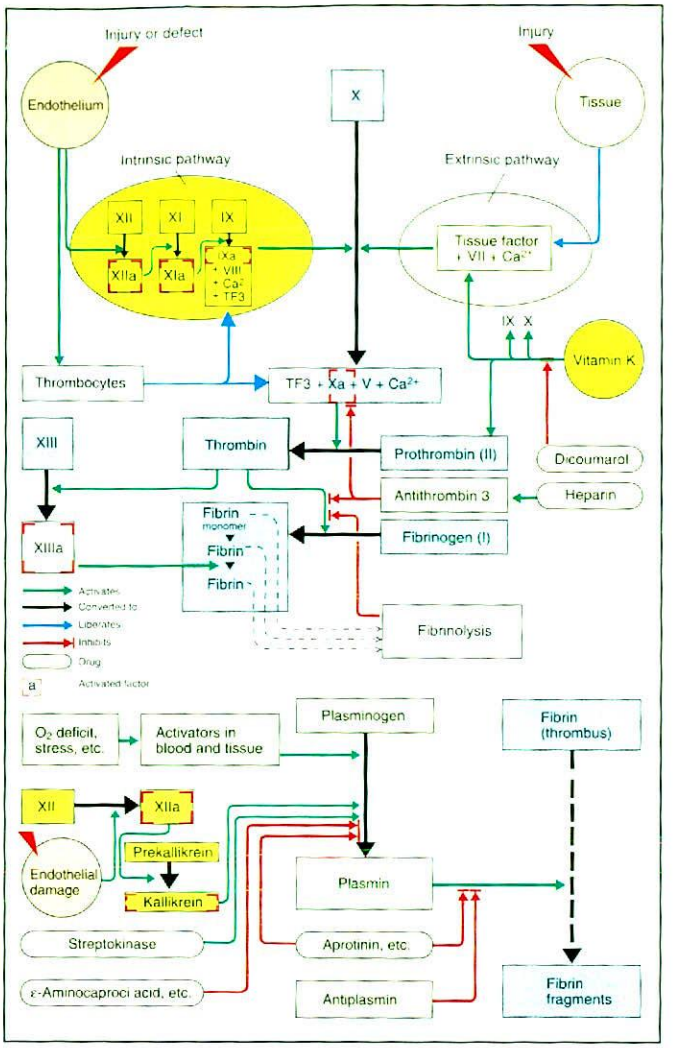
B. Cells involved in Immune system



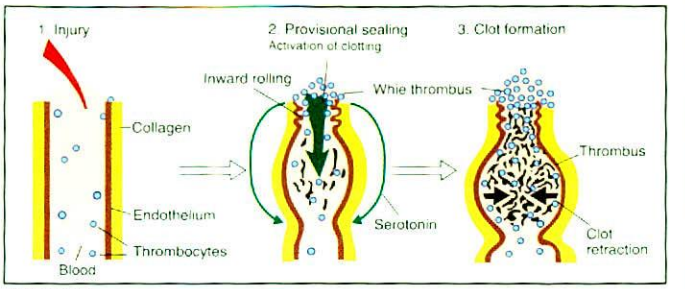
C. Stimulation of the B-lymphocytes ; humoral immune defense



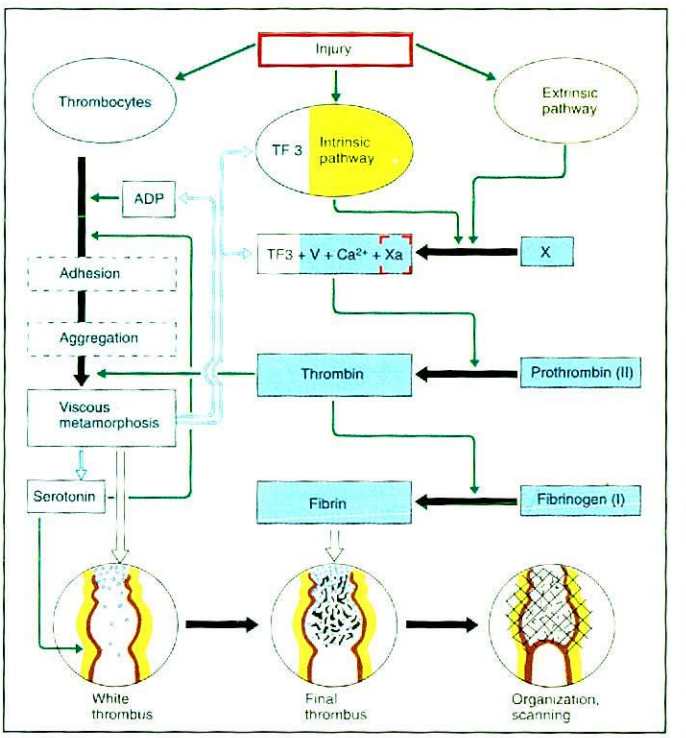
D. Stimulation of the T-lymphocytes and activation of macrophages



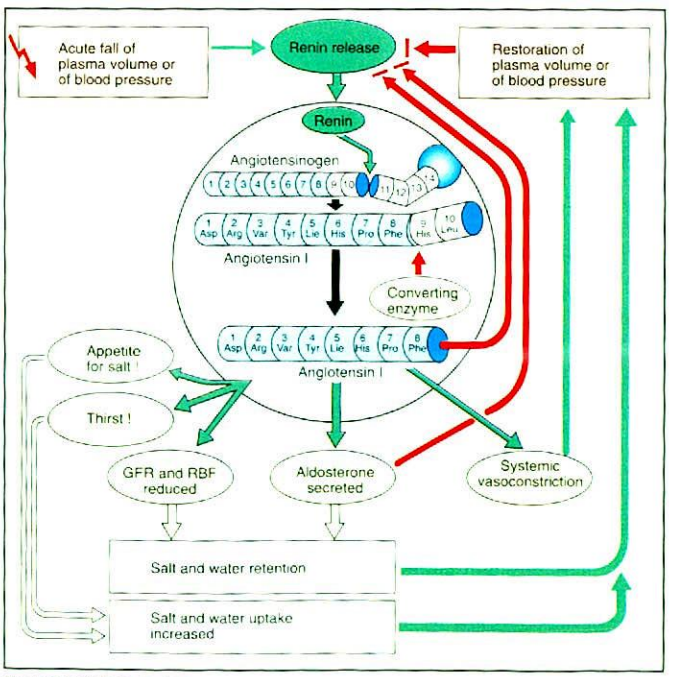
Blood clotting and fibrinolysis



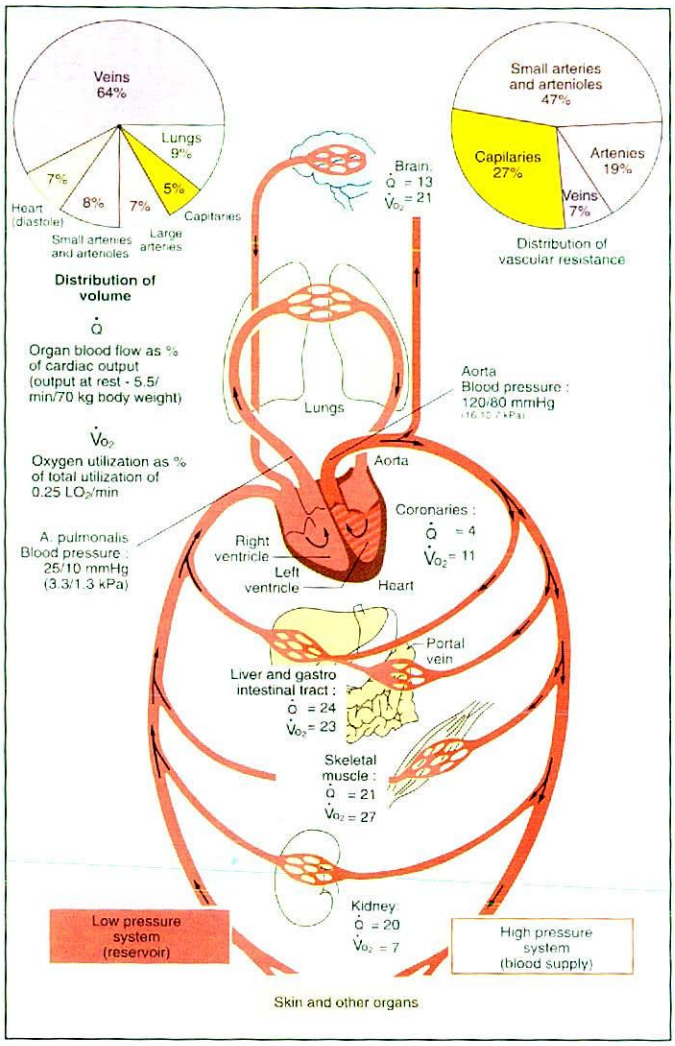
Hemostasis



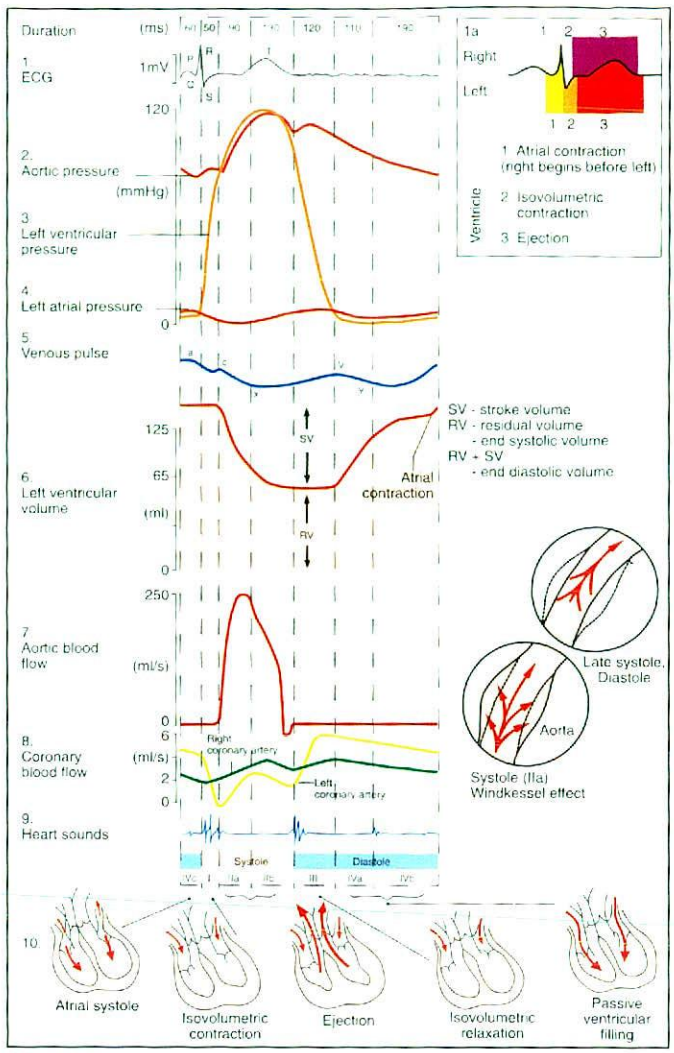
Hemostasis



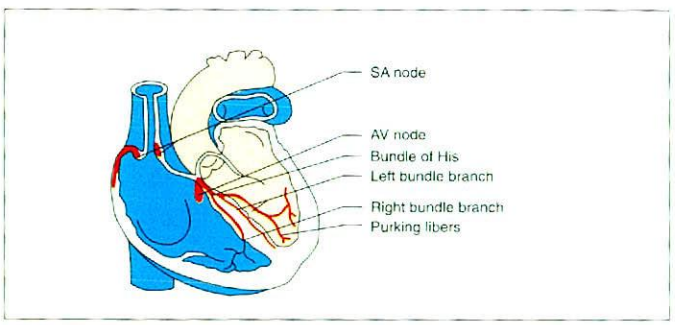
Renin-anglotensin system



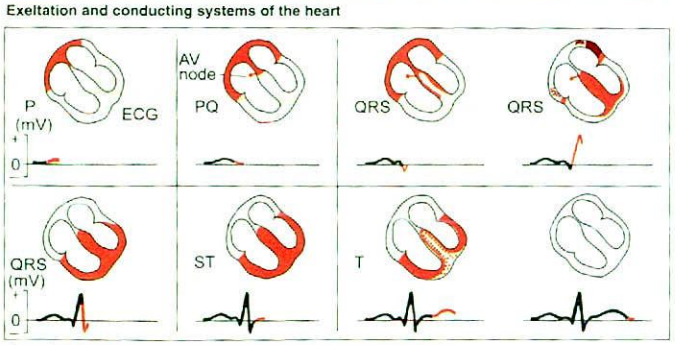
Cardiovascular system



Cardiac cycle



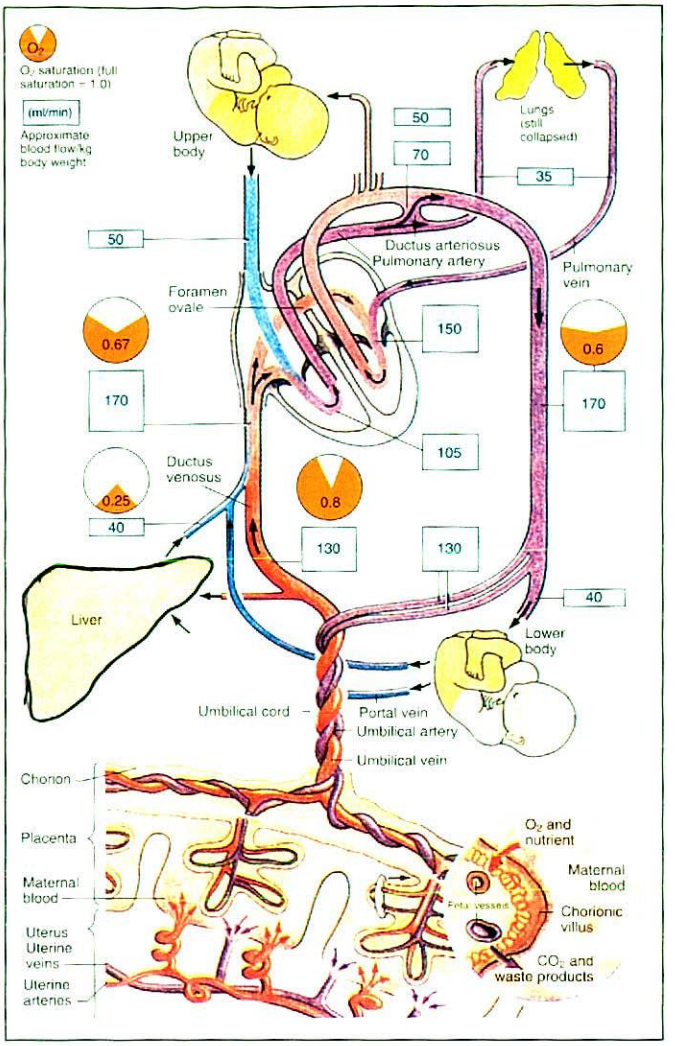
Exeltation and conducting systems of the heart



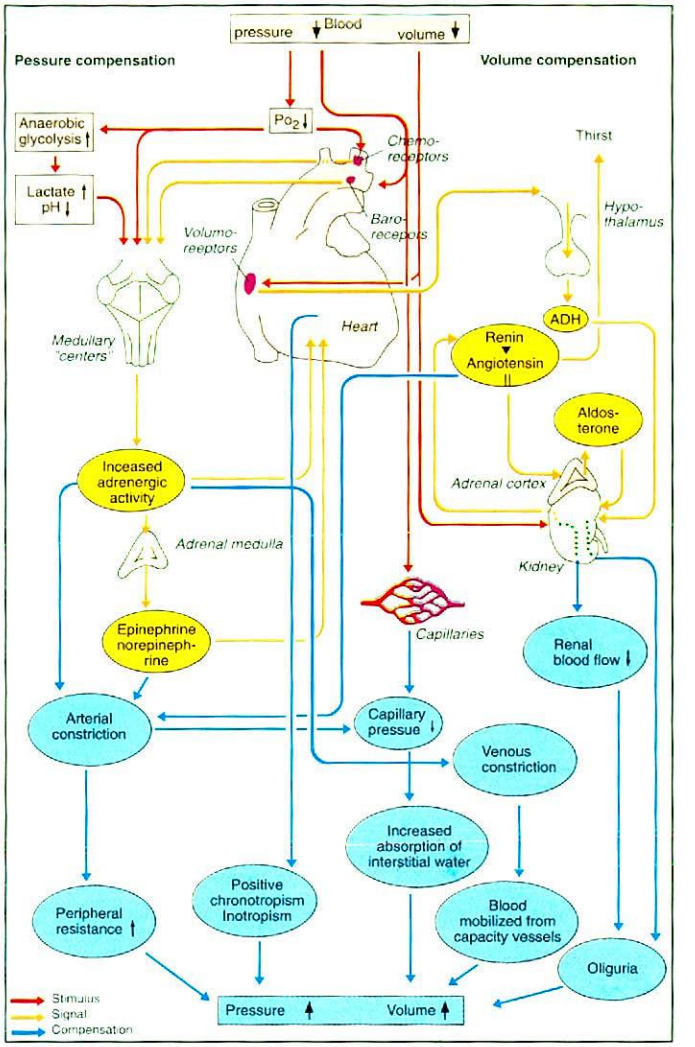
Correlation of ECG with de-and repolarization wave in the heart

Event		Time (ms)	ECG	Conduction velocity (m/s)	Intrinsic automaticity (min⁻¹)
SA node					
Impulse generated		0	Pwave	0.05	70-80
Atrial depolarization	right	50		0.8-1.0	
	left	85			40-60
AV node					
Arrival of Impulse		50	P.Q Interval (delay in excitation)	0.05	
Departure of Impulse		125		1.0-1.5	
Bundle of His activated		130		1.0-1.5	
Bundle branches activated		145		3.0-3.5	
Purkije fibers activated		150			
Endooardium depolarized	right ventriele	175	QRS complex	1.0 in myocardium	20-40
	left ventricle	190			
Myeeardluum depolarized	right ventricle	205			
	left ventricle	225			

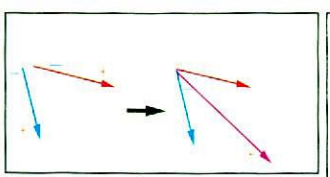
Excitation of the heart : time course, ECG and conduction velocity



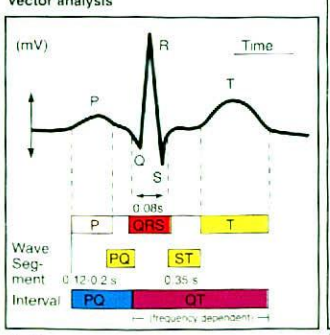
Fetal circulation and placenta



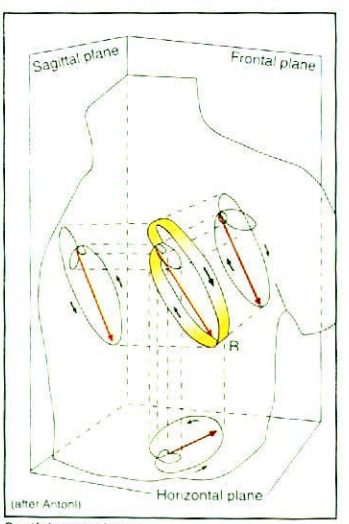
Compensatory responses in reversible hypovolemic shock



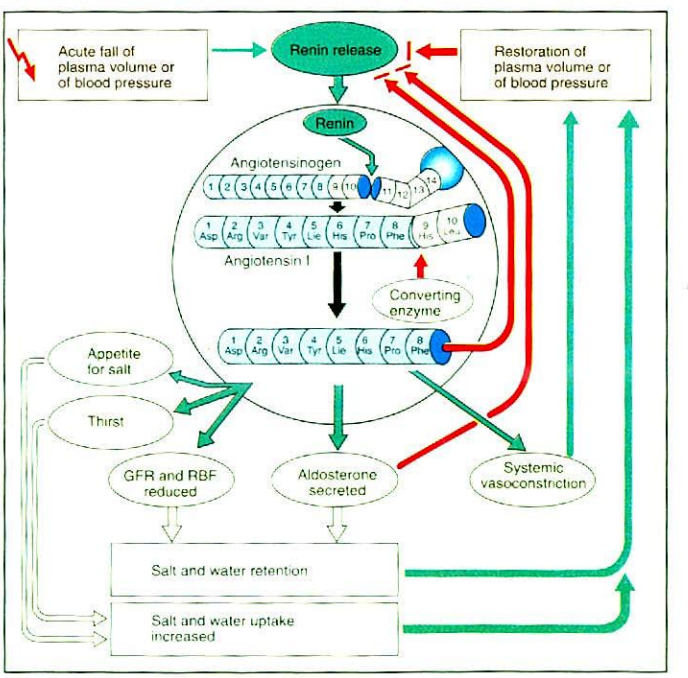
Vector analysis



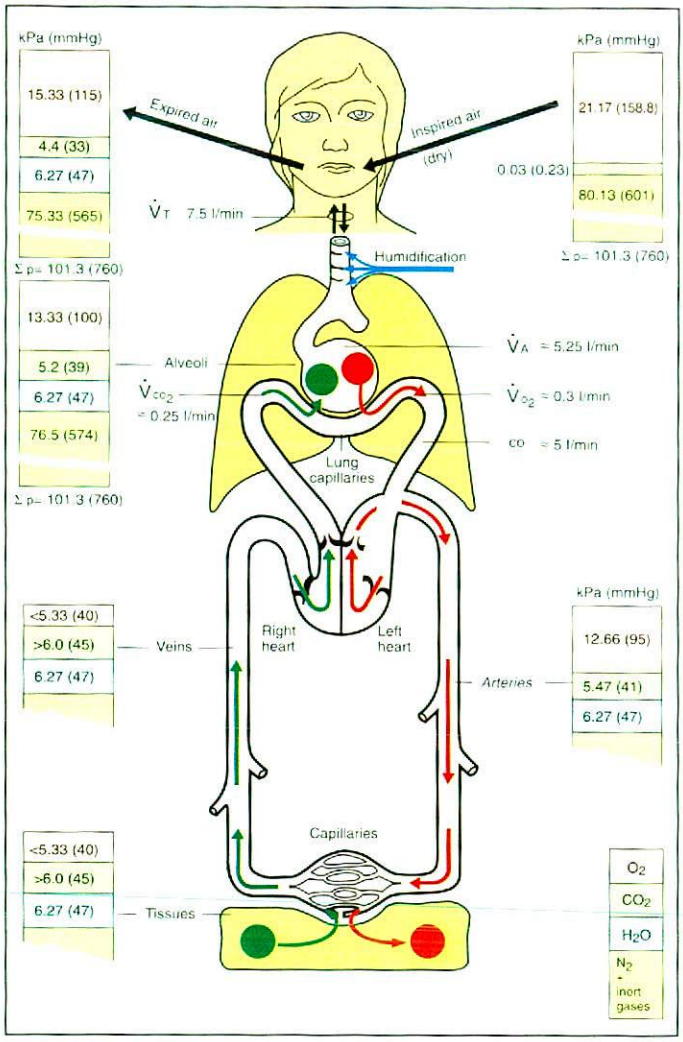
ECG



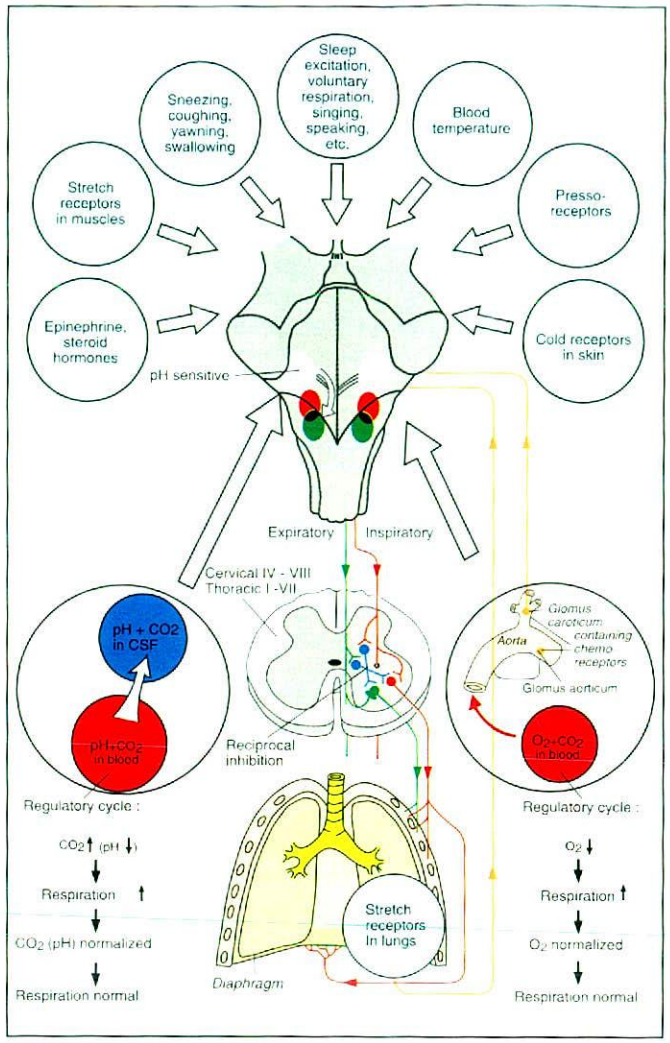
Spatial vector loops



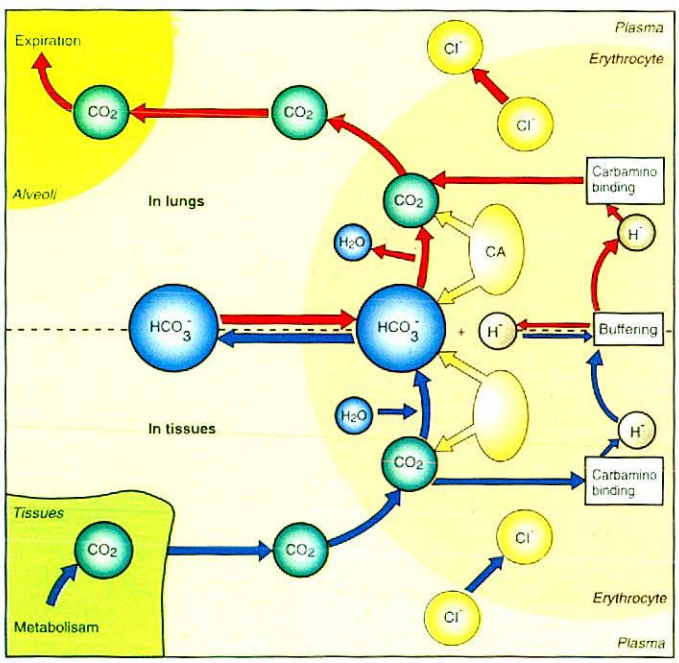
Renin-anglotensin system



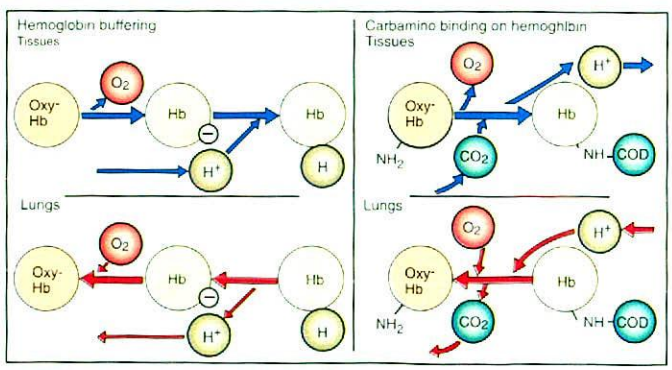
Respiration



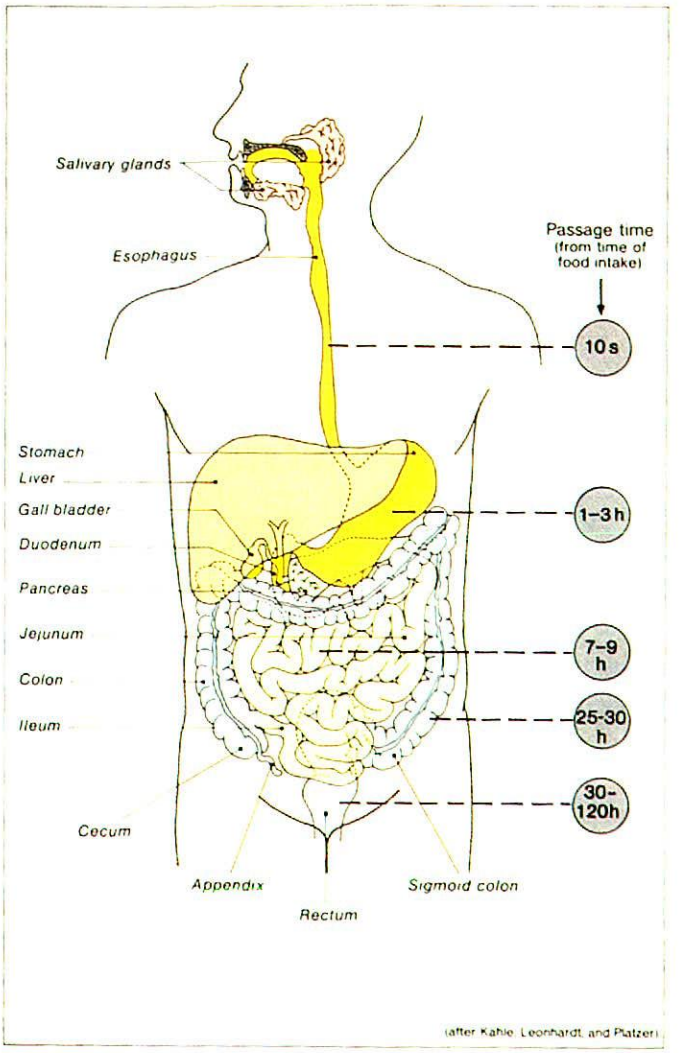
Respiratory " centers" and Influences



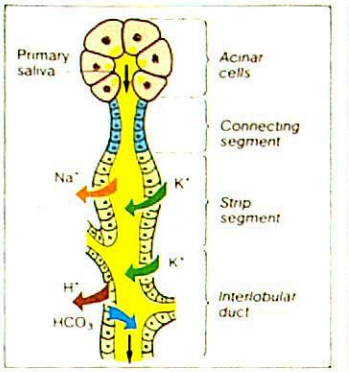
CO_2 transport



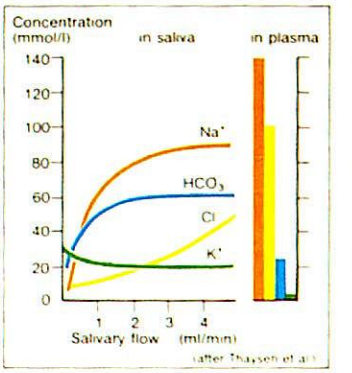
Buffering and carbamino binding in erythrocytes



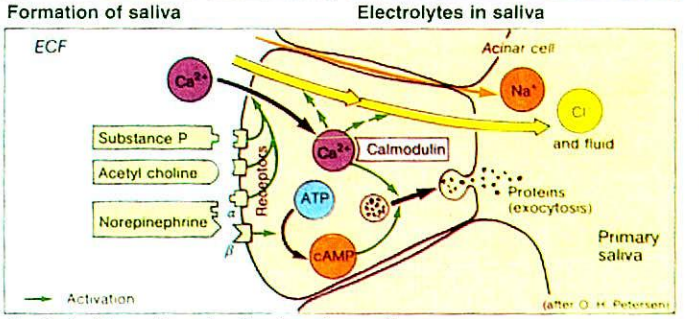
Gastrointestinal tract; organs and passage time



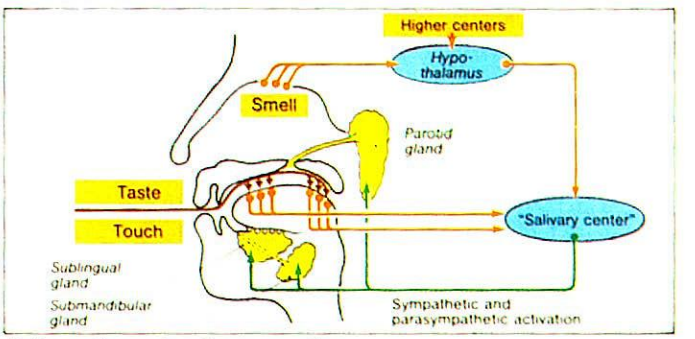
Formation of saliva



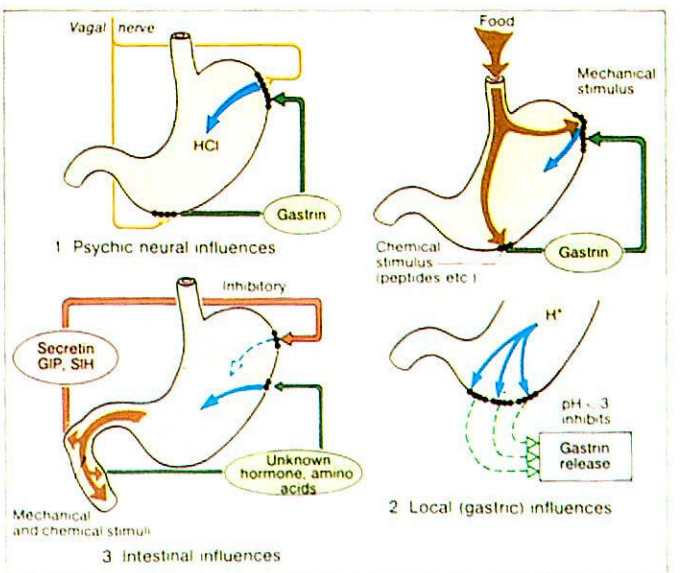
Electrolytes in saliva



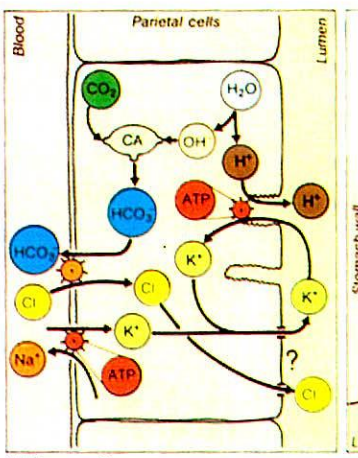
Control of formation of saliva in acinar cells



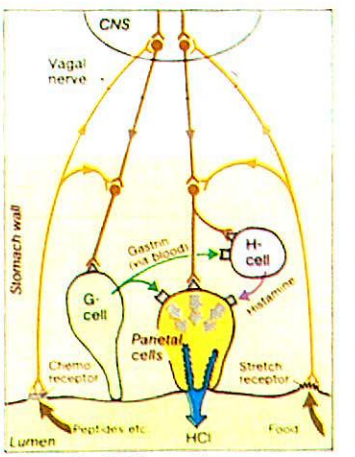
Reflex pathways in salivary secretion



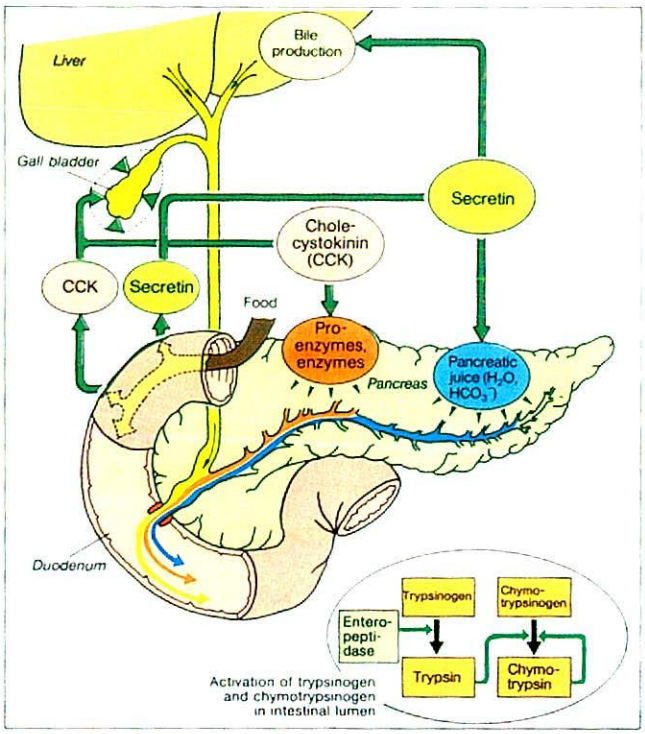
Secretion of gastric juice



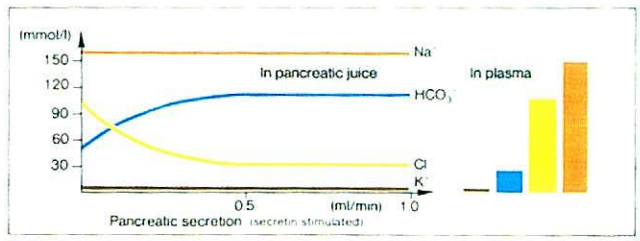
HCl secretion



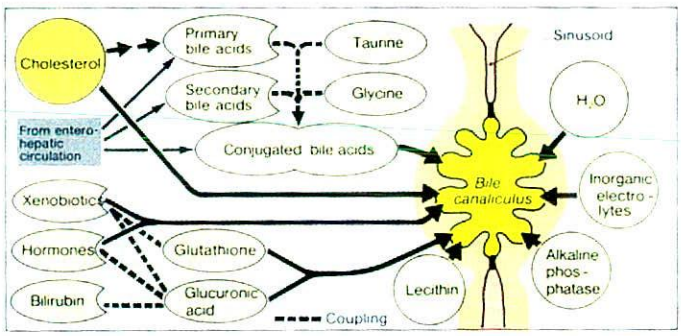
Control of HCl secretion



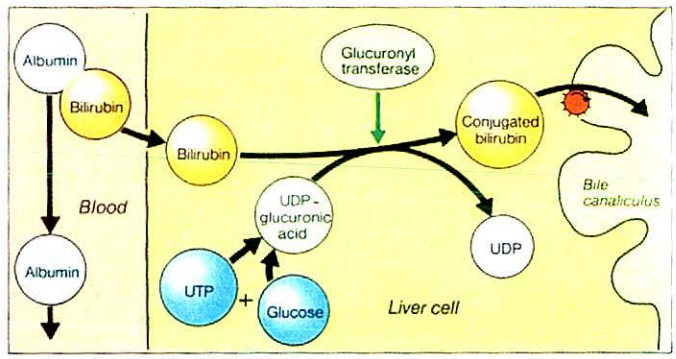
Bile and pancreatic juice



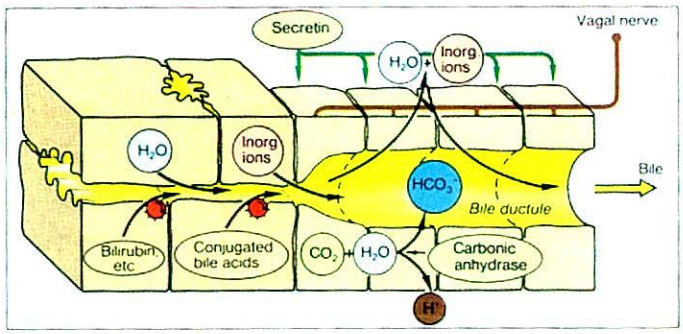
Electrolyte concentrations in pancreatic juice



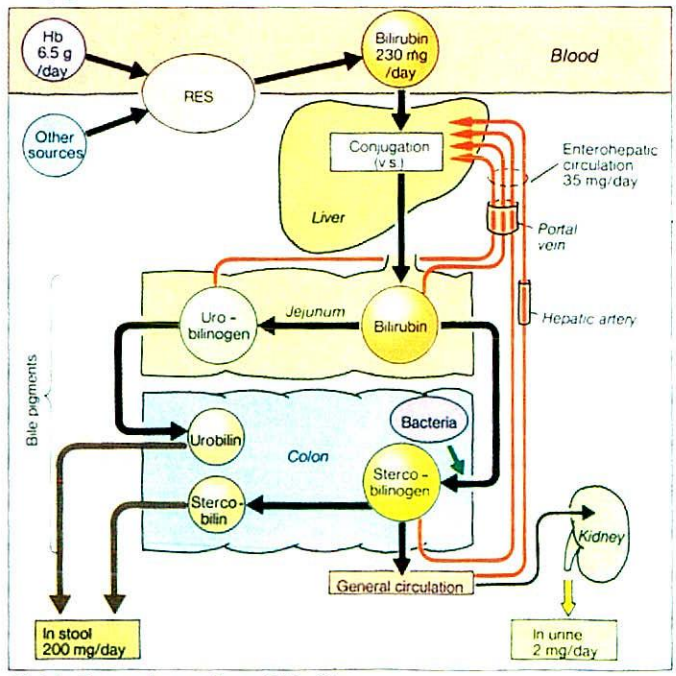
Excretory functions of liver



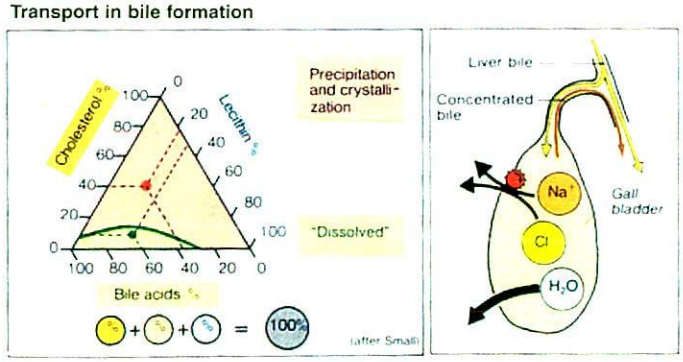
Conjugation of bilirubin in the liver



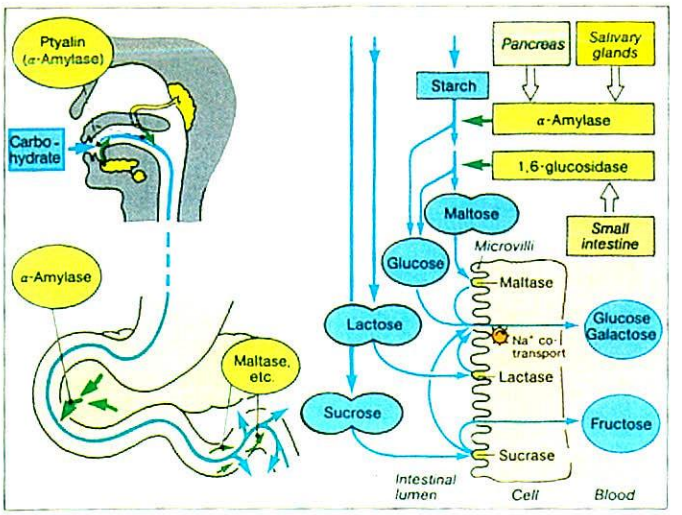
Transport in bile formation



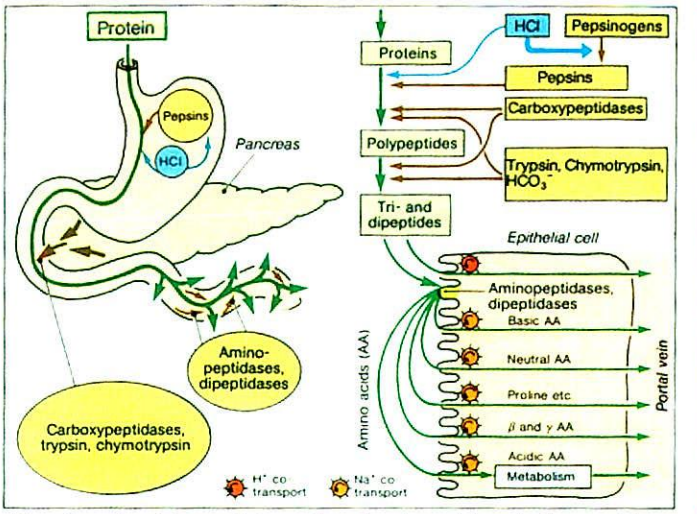
Metabolism and excretion of bilirubin



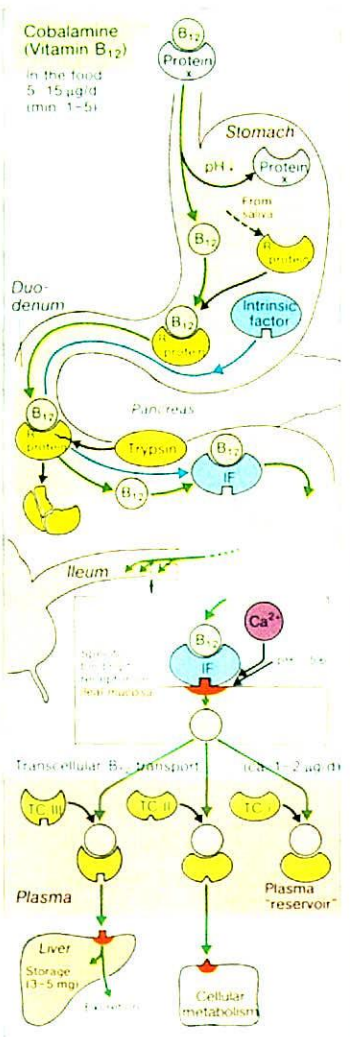
Micellar solution of cholesterol in bile



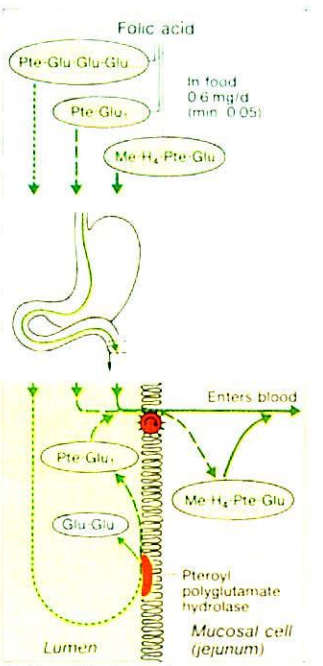
Digestion of carbohydrates and absorption of monosaccharides



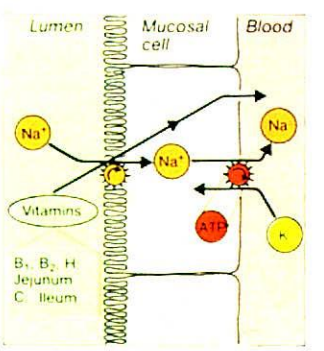
Digestion of proteins and absorption of amino acids and oligopeptides



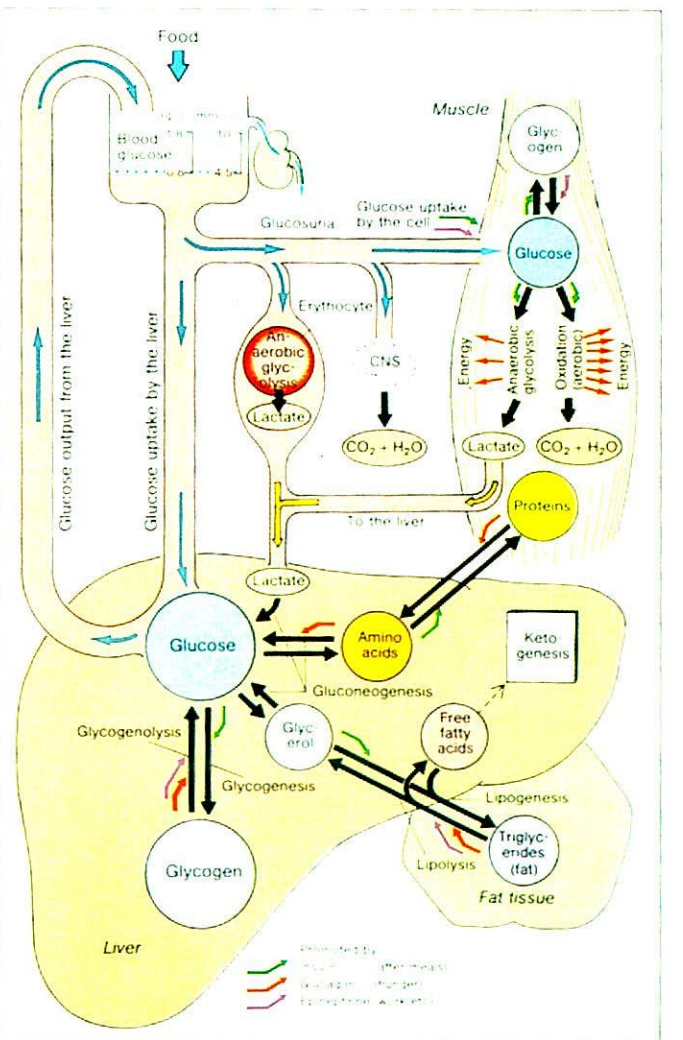
Cobalamine (B_{12}) transport



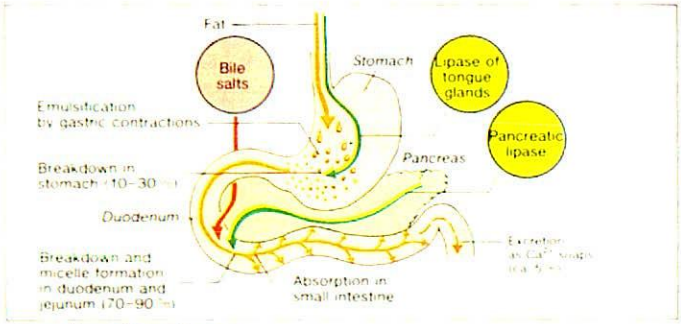
Folic acid absorption



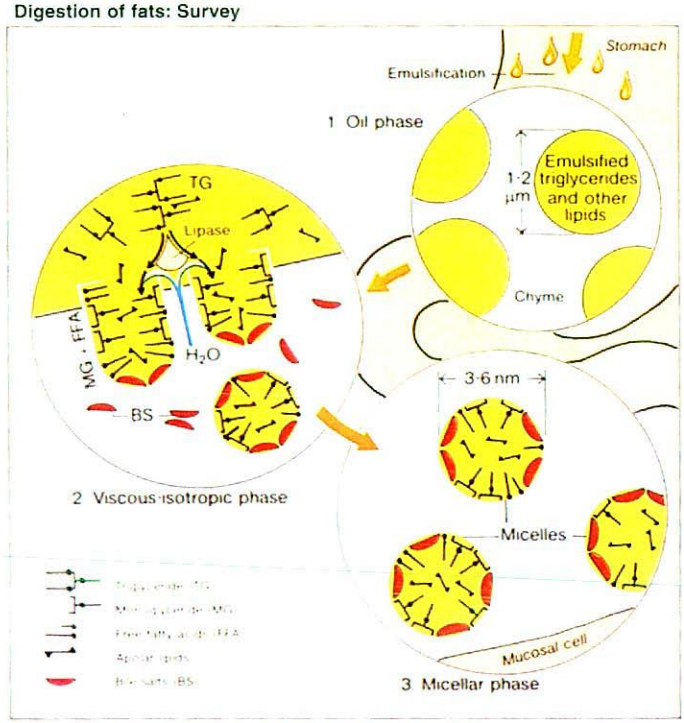
Secondary active vitamin absorption



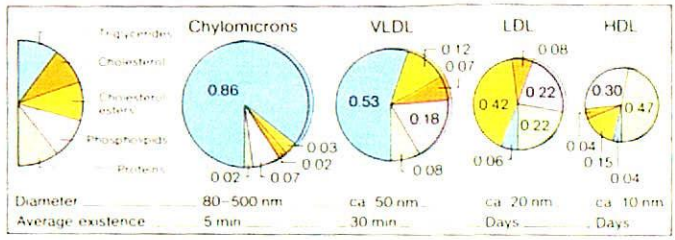
Glucose metabolism (simplified)



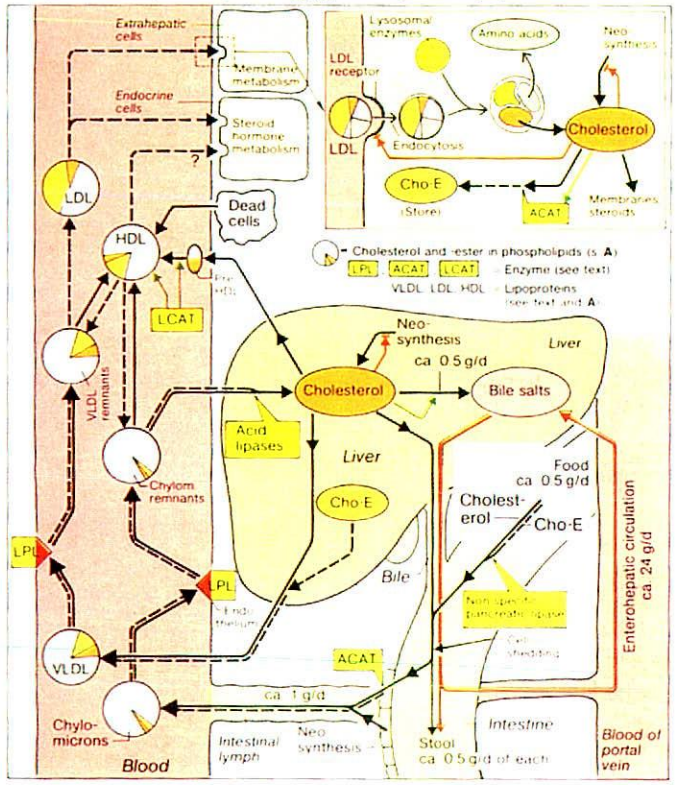
Digestion of fats: Survey



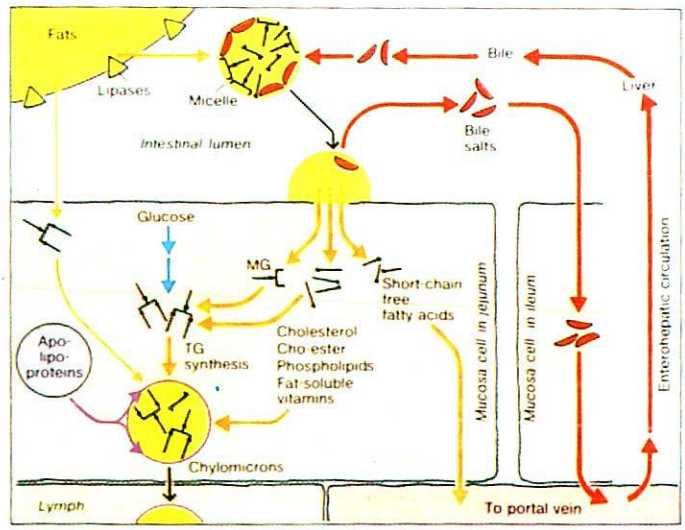
Digestion of fats: Breakdown and micelle formation (after Patton)



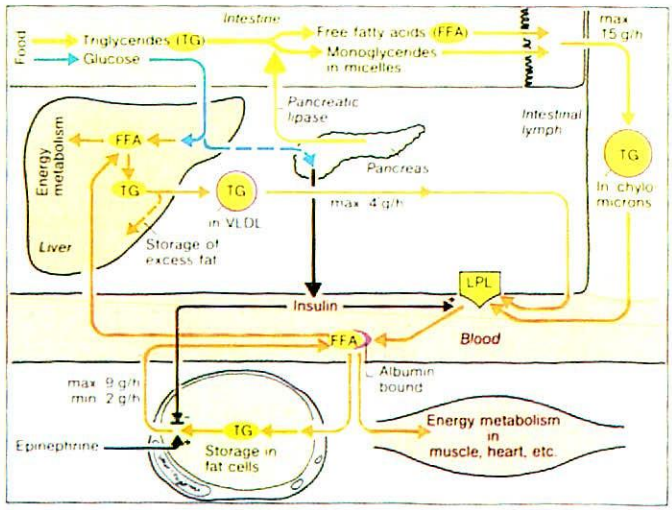
Proportion of lipid and protein (g/g) in the plasma lipoproteins



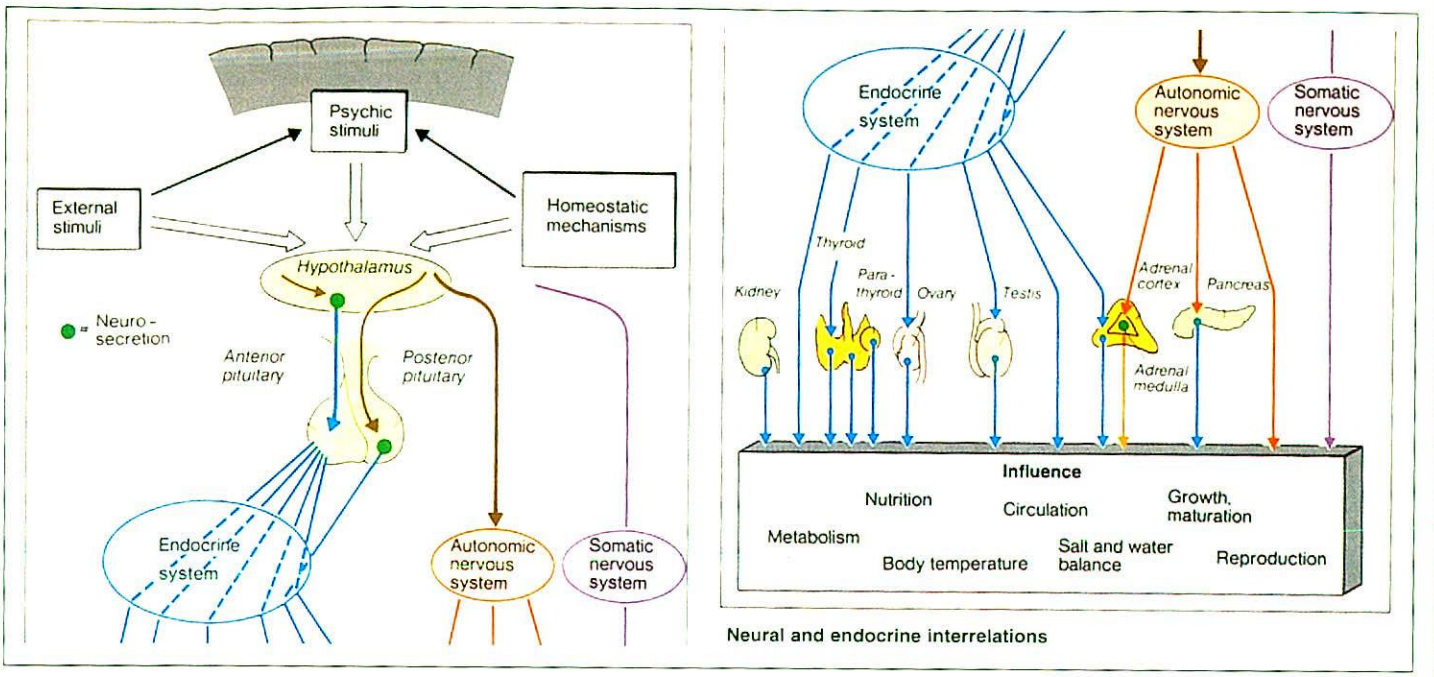
Sources and fate of cholesterol



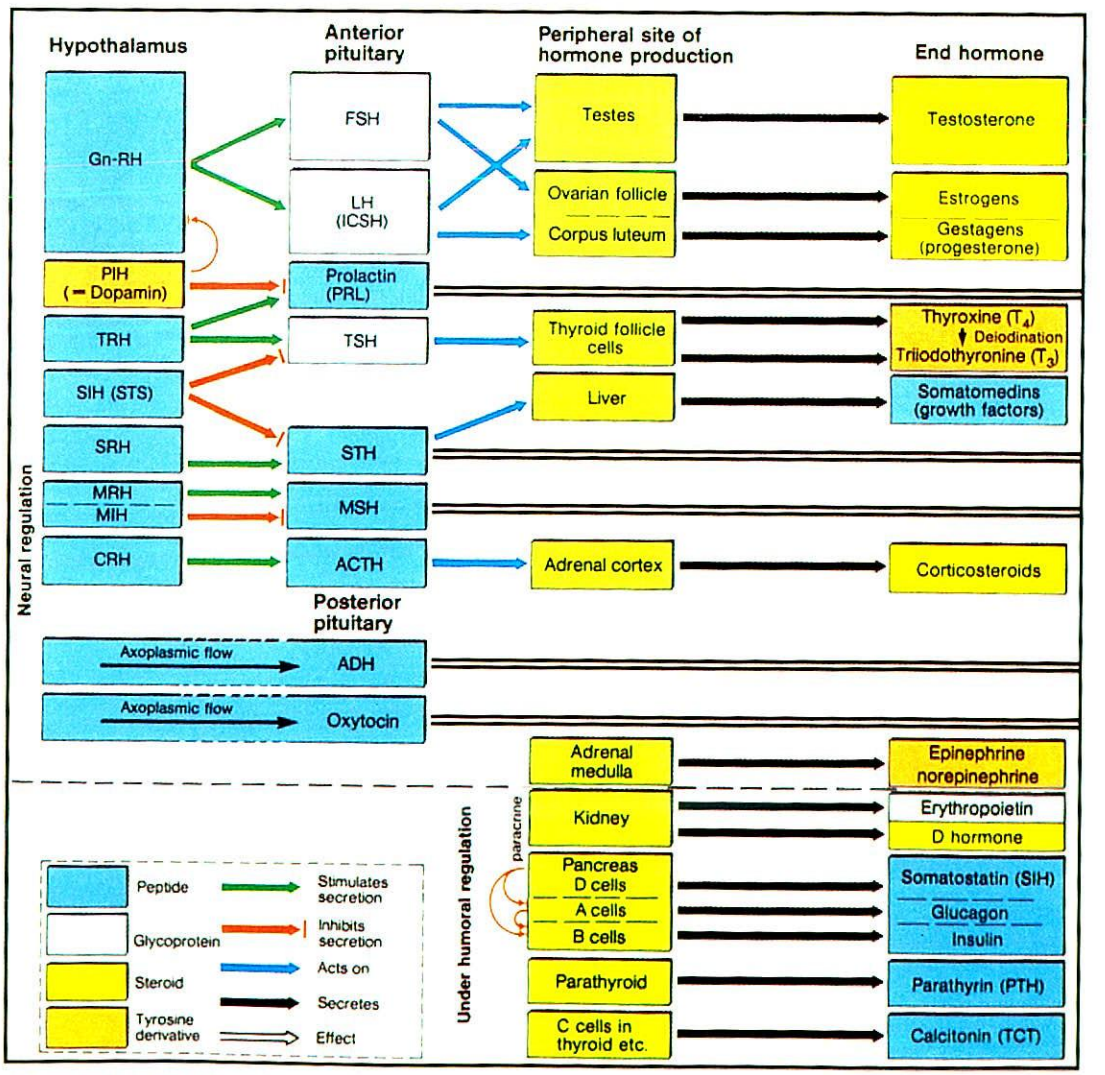
Absorption of fats



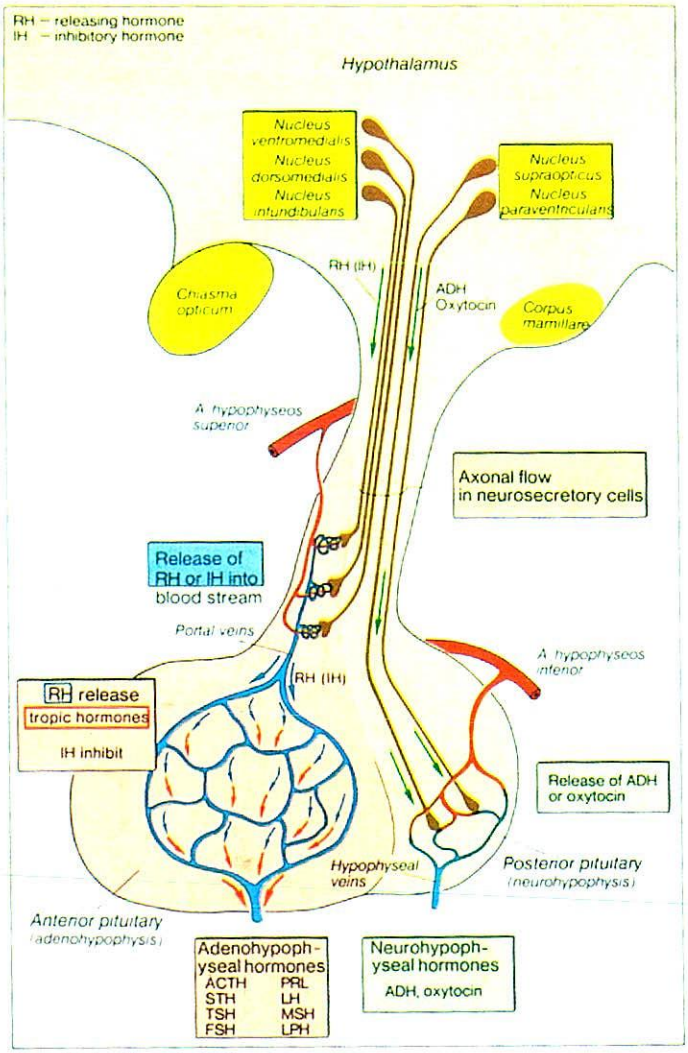
Sources and fate of triglycerides and free fatty acids



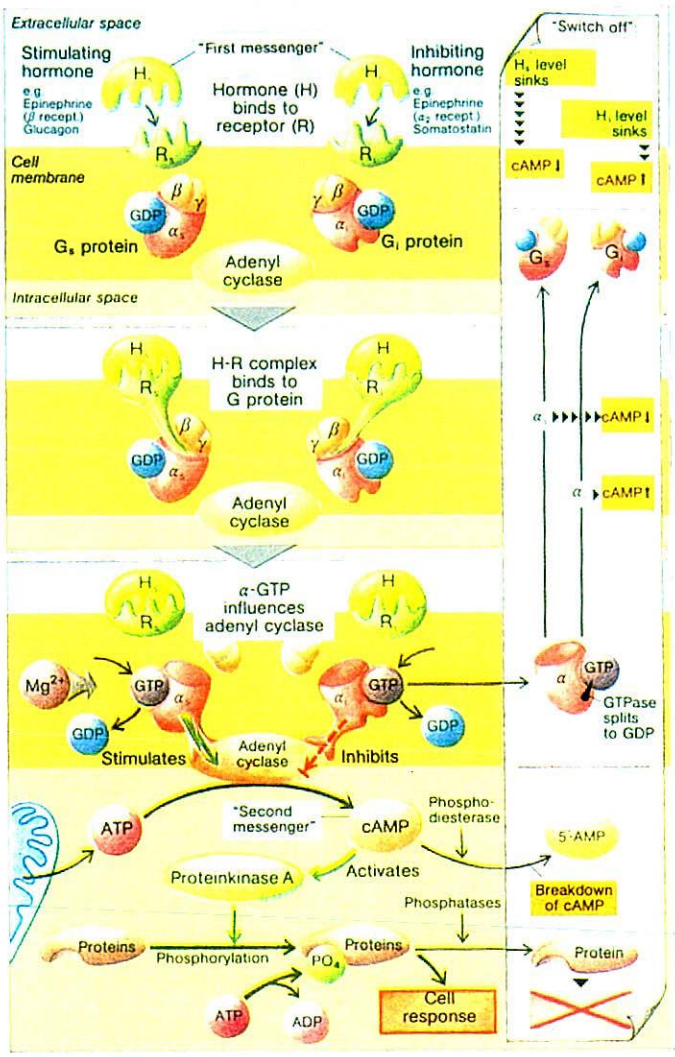
Neural and endocrine interrelations



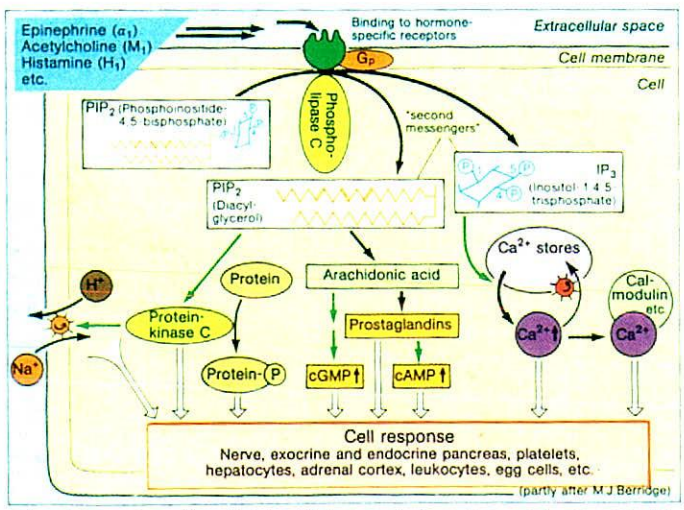
Hormones (excluding tissue hormones)



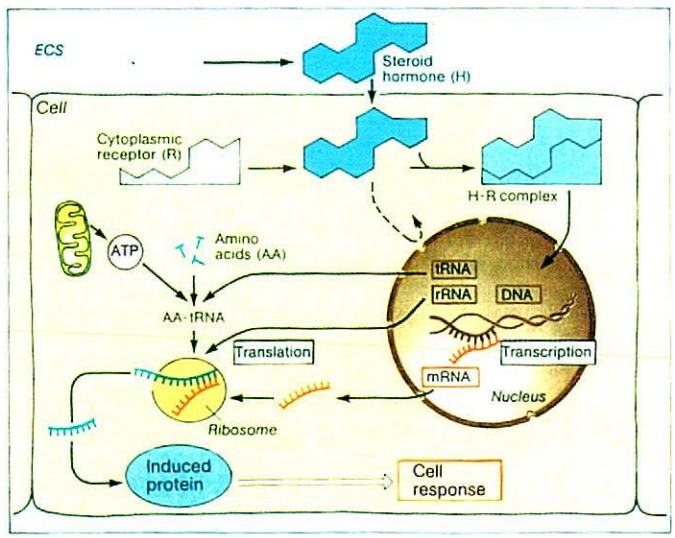
Hypothalamic and pituitary hormones



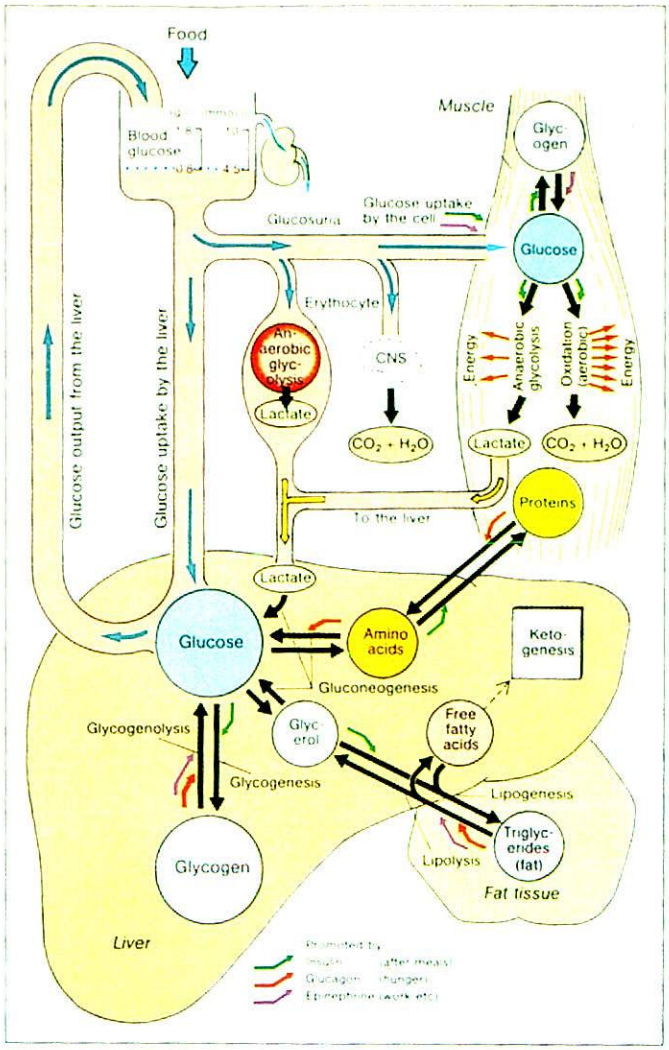
cAMP as "second messenger"



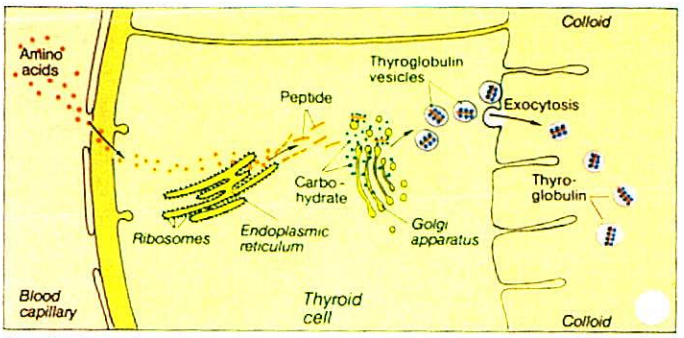
Diacylglycerol and inositol-1,4,5-trisphosphate as "second messengers"



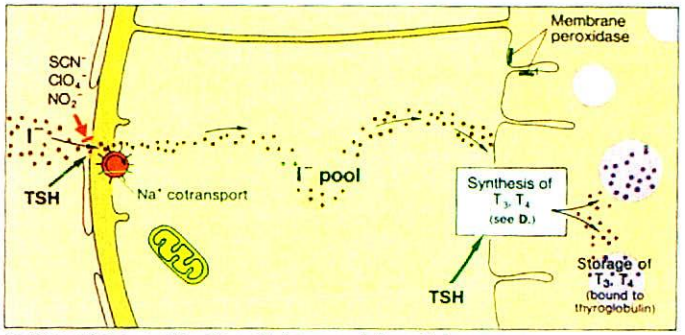
Mechanism of action of steroid hormones



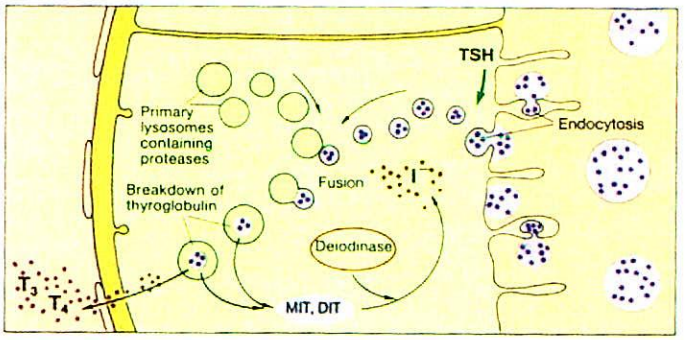
Glucose metabolism (simplified)



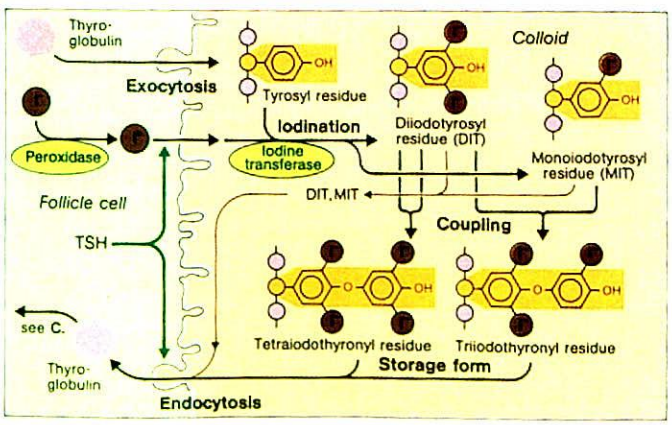
Synthesis of thyroglobulin



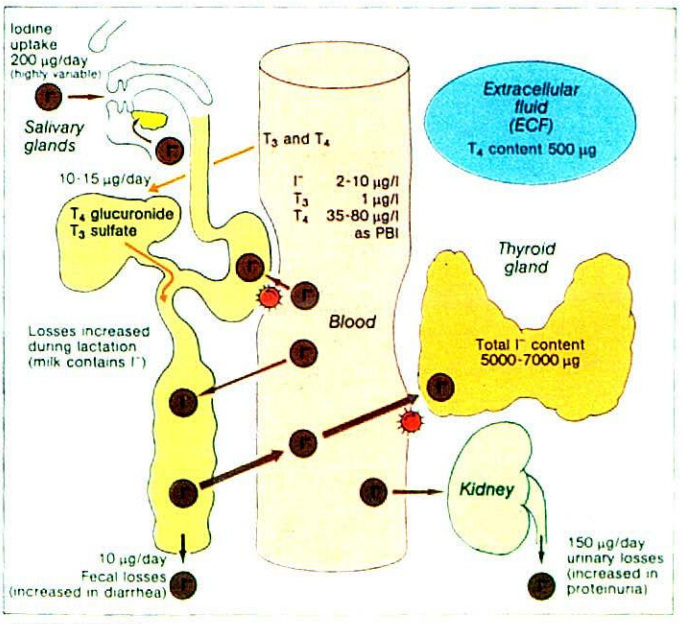
Iodine uptake, synthesis and storage of thyroid hormones



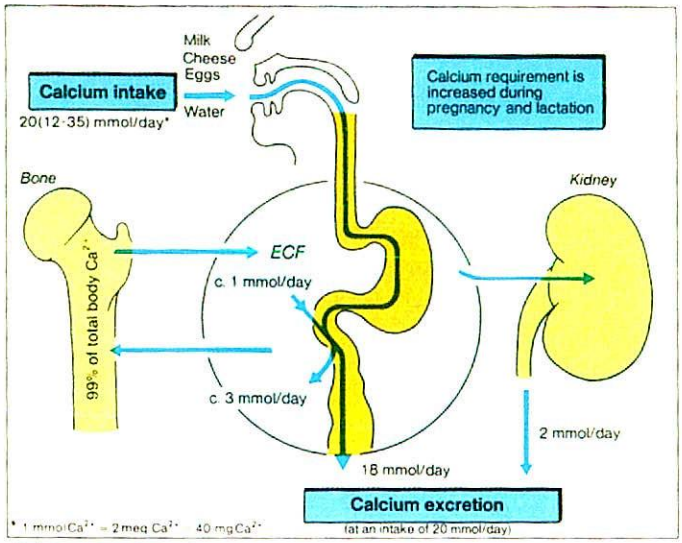
Secretion of thyroid hormones



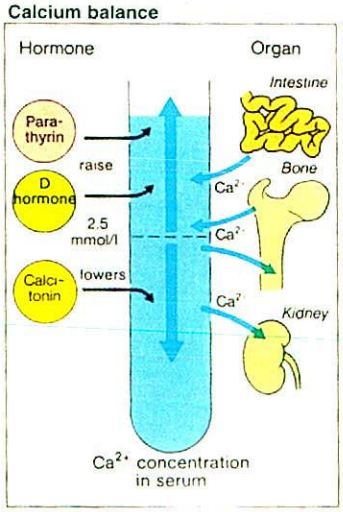
Synthesis, storage and mobilization of the thyroid hormones



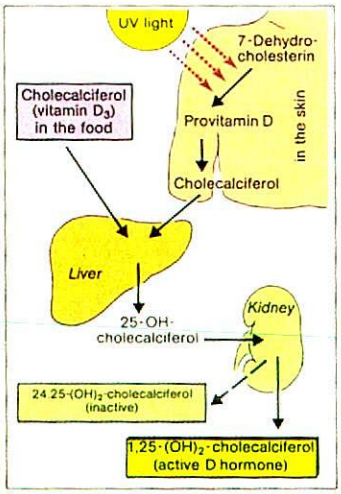
Iodine balance



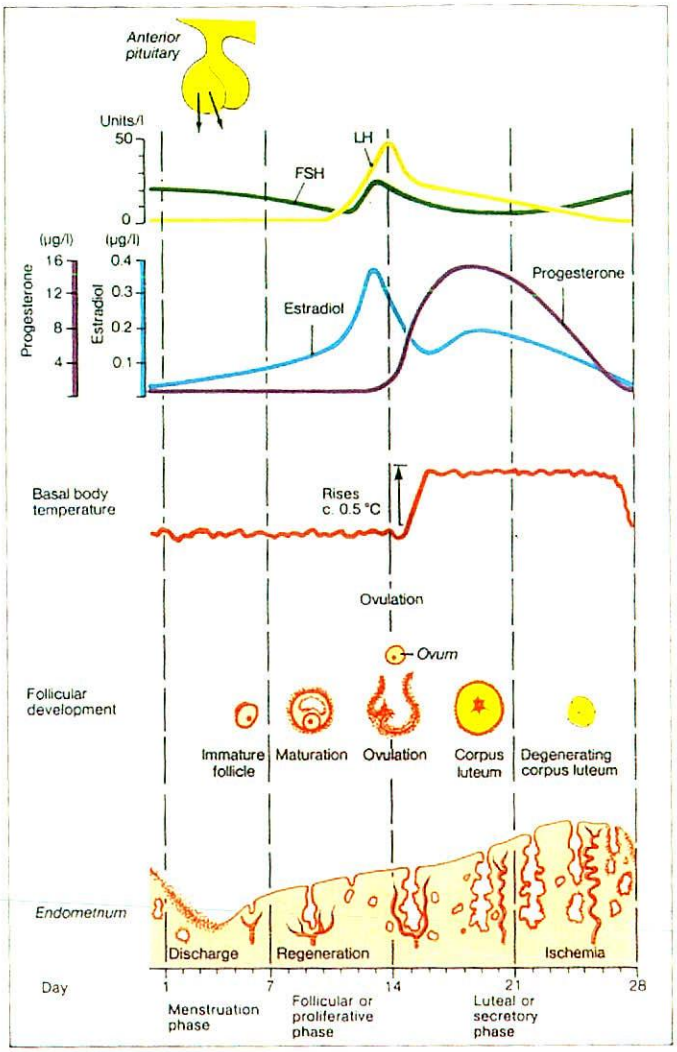
Calcium balance



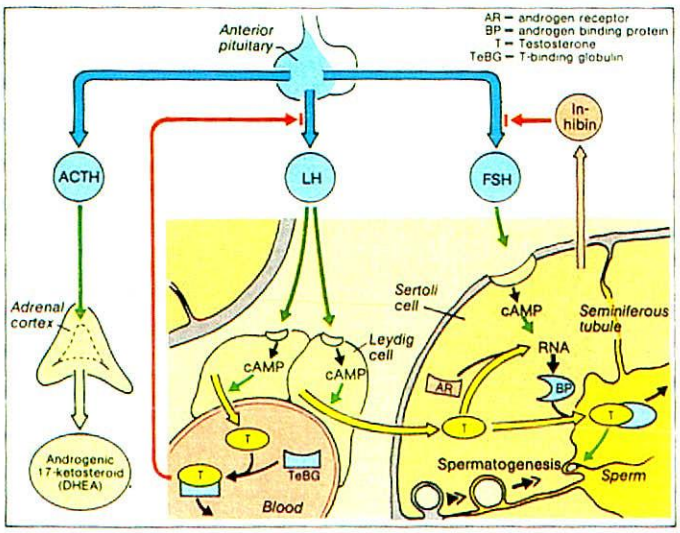
Influences on Ca^{2+} serum levels



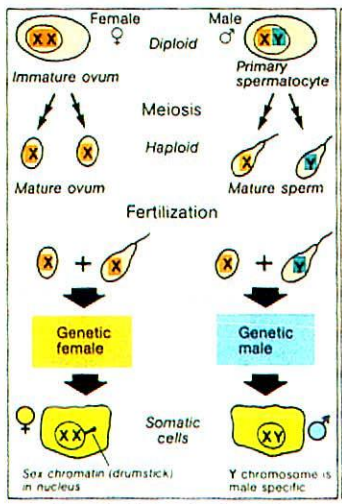
Formation of the D hormone



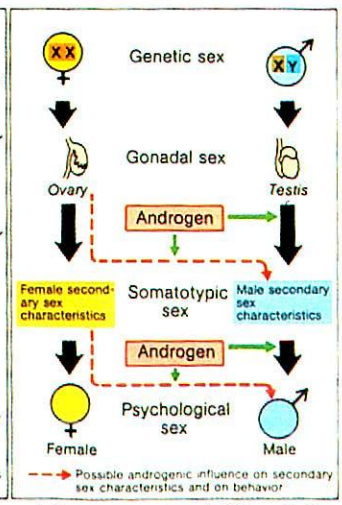
Human menstrual cycle



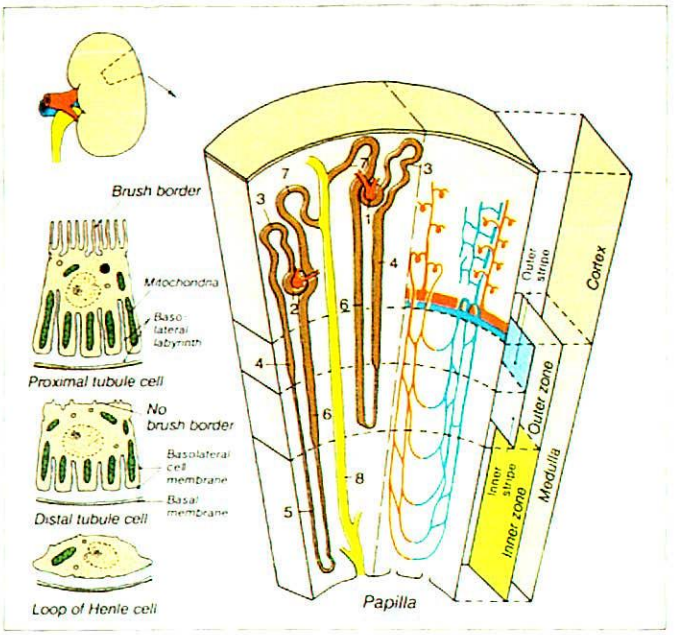
Control and transport of androgenic hormones. Effects of testosterone.



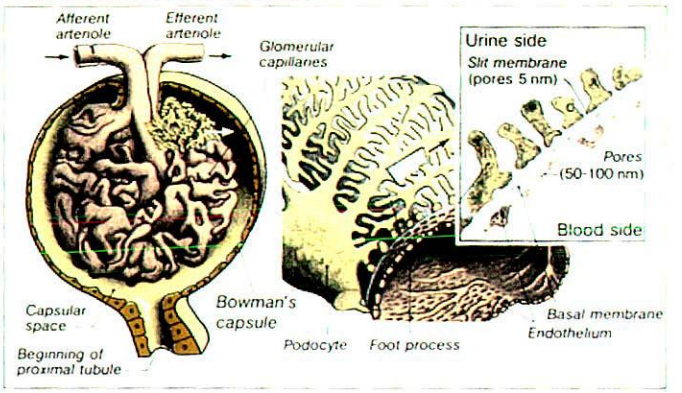
Genetic determination of sex



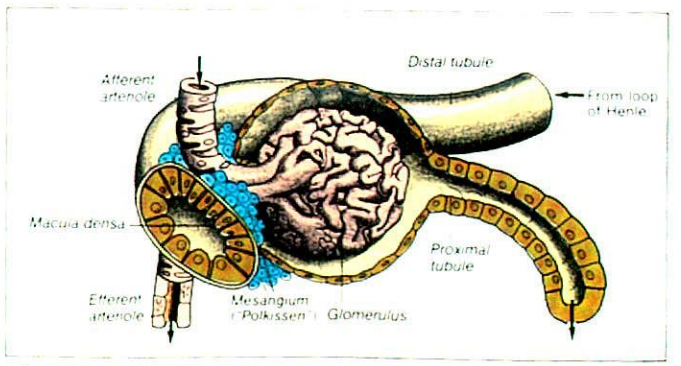
Influences on sexual differentiation



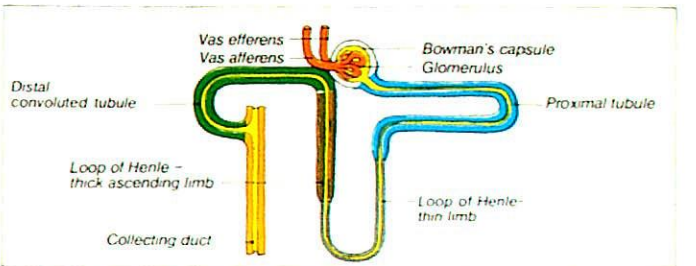
Functional anatomy of the kidney



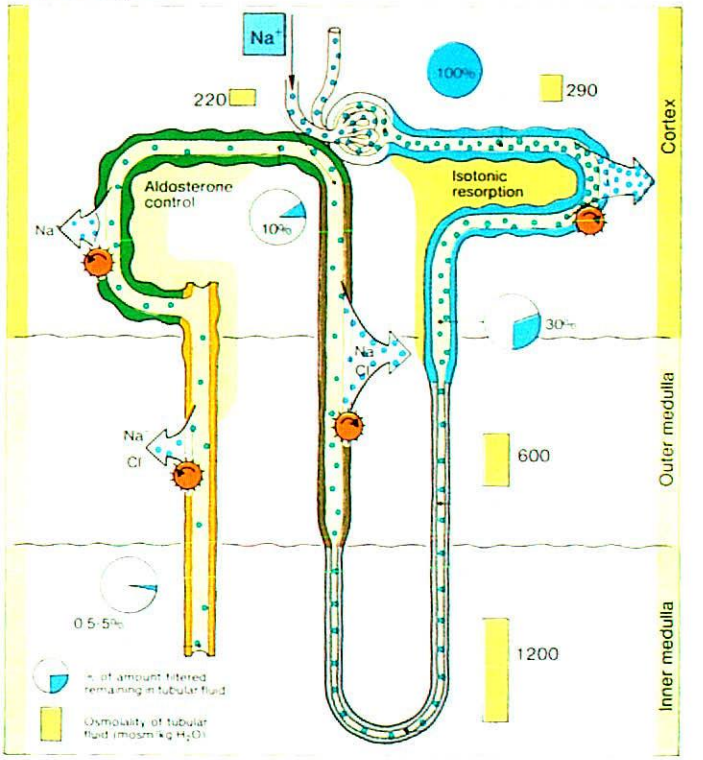
Glomerulus and Bowman's capsule



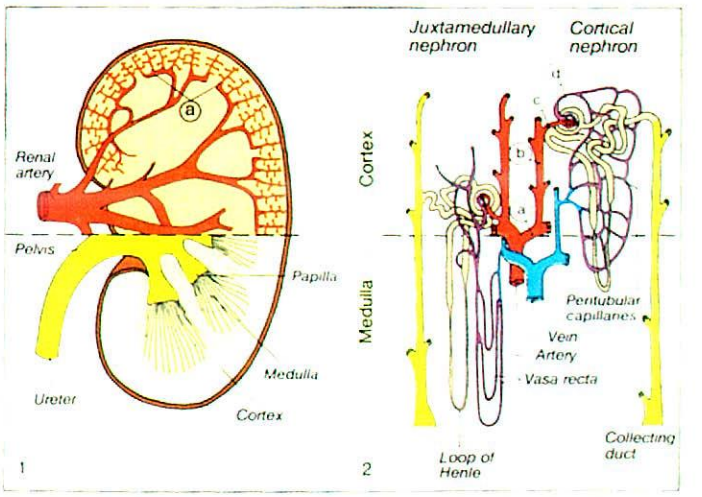
Juxtaglomerular apparatus



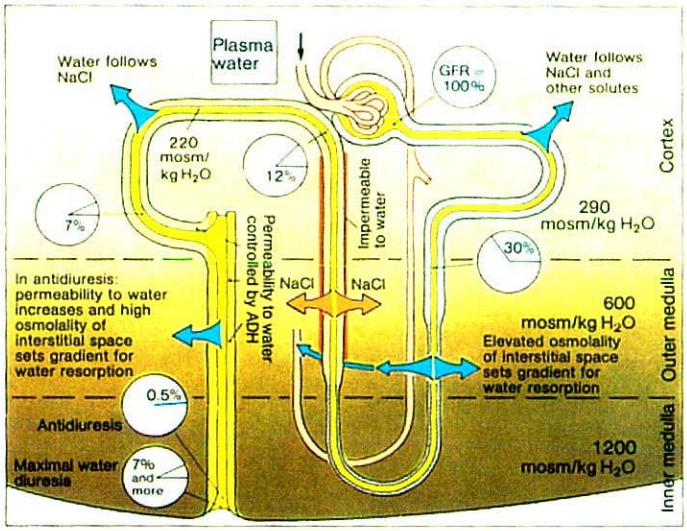
Nephron segments



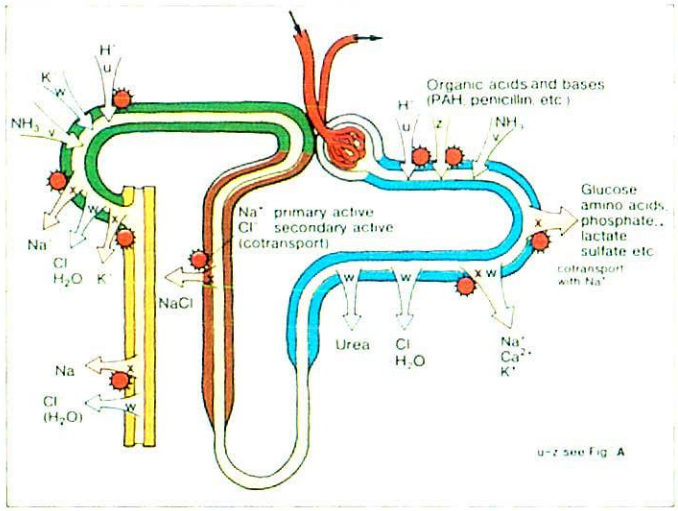
Na+ resorption in the nephron



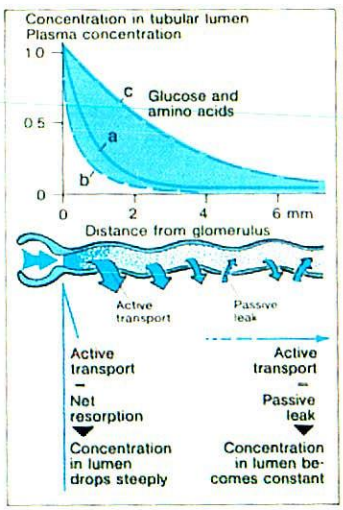
Vascular arrangement in kidney



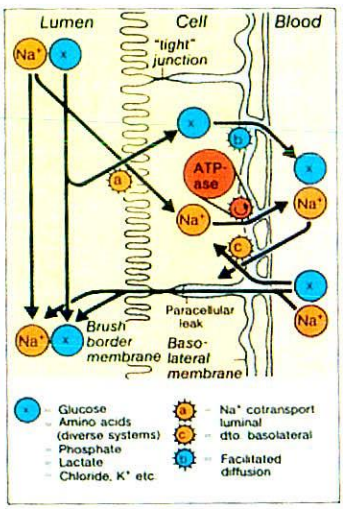
Fluxes of water in the nephron



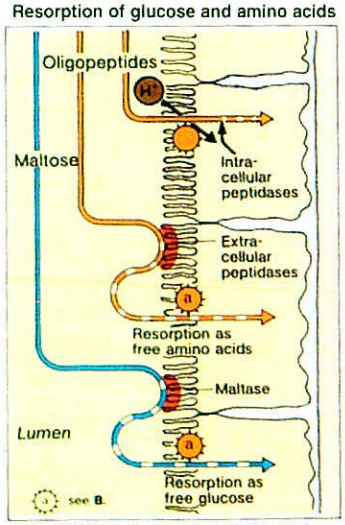
Locus of transport processes in the nephron (simplified)



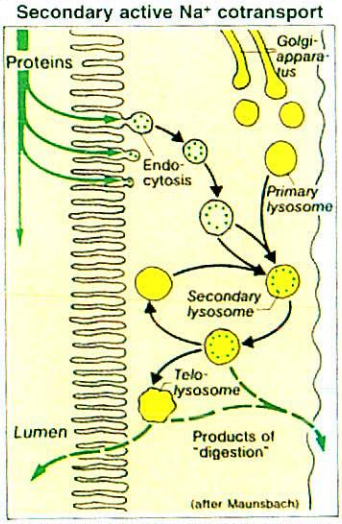
Resorption of glucose and amino acids



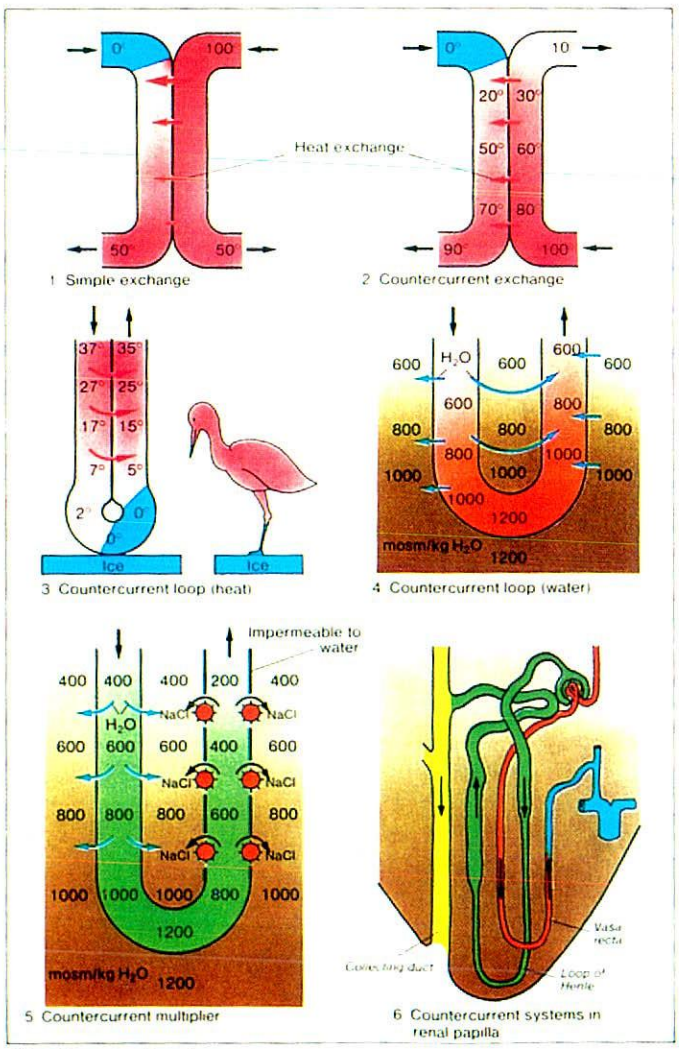
Secondary active Na^+ cotransport



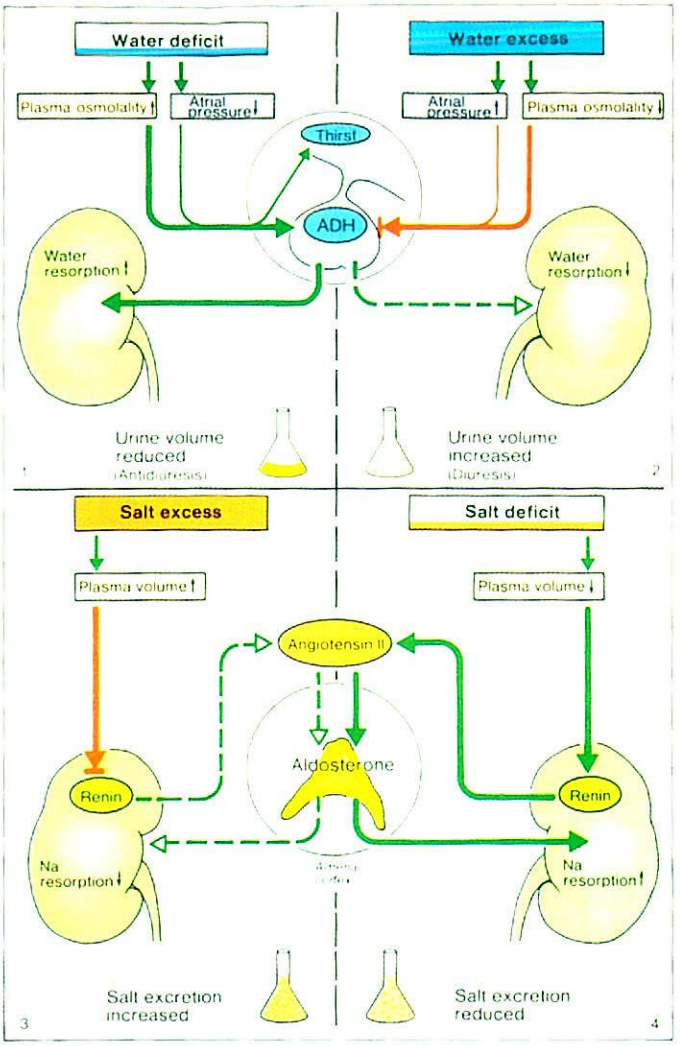
Resorption of oligopeptides and maltose



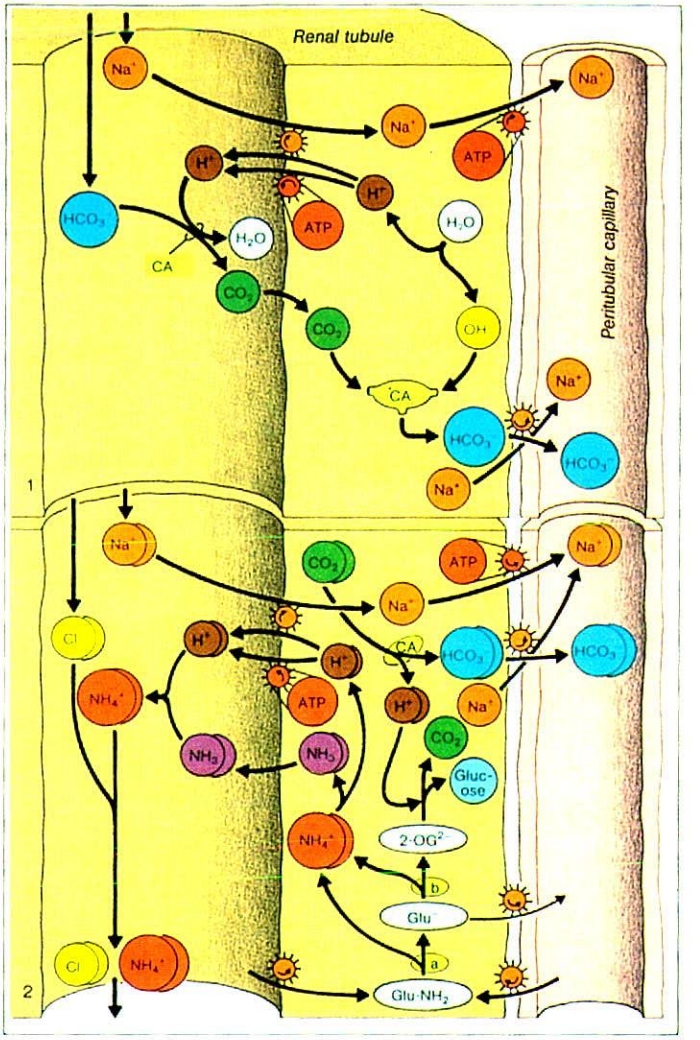
Protein resorption by endocytosis



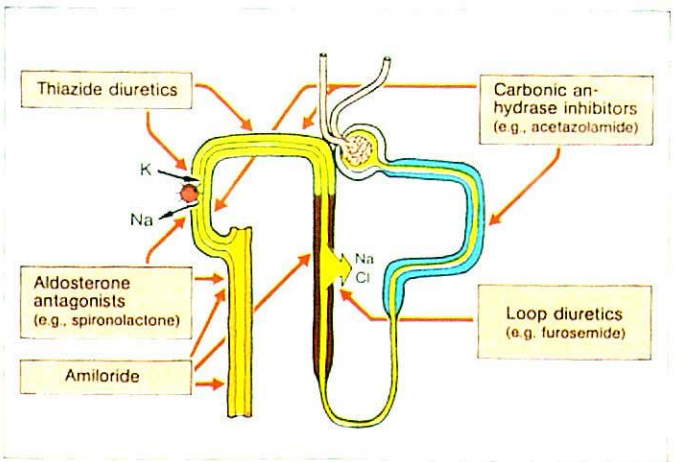
Countercurrent systems



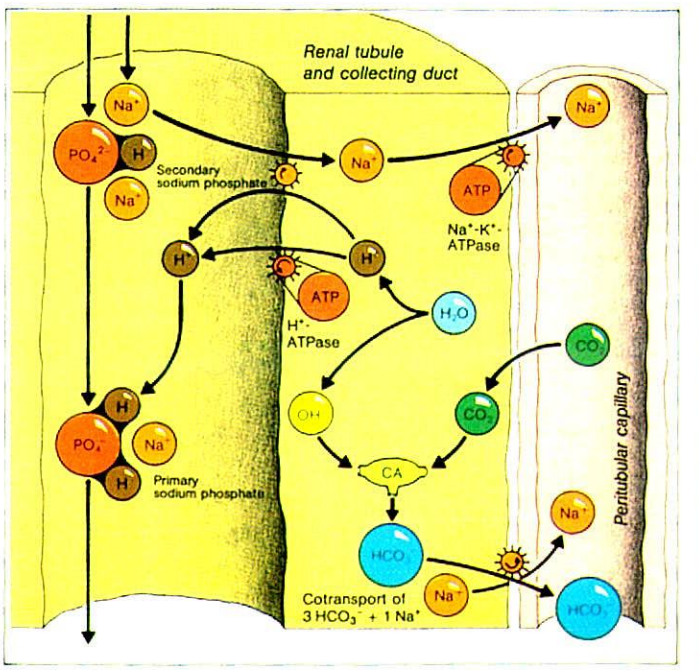
Hormonal control of salt and water balance



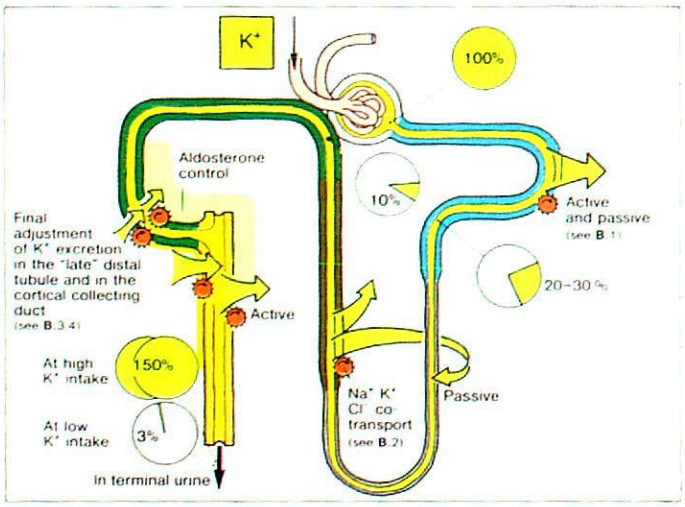
Bicarbonate resorption (1) and NH_4^+ excretion (2)



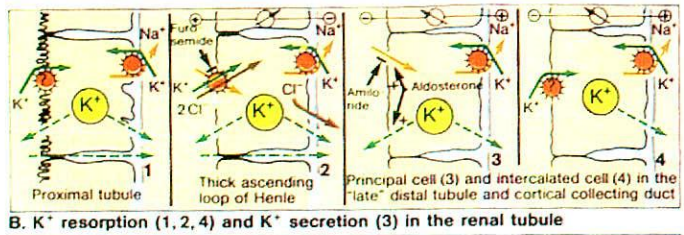
Locus of action of diuretics (simplified)



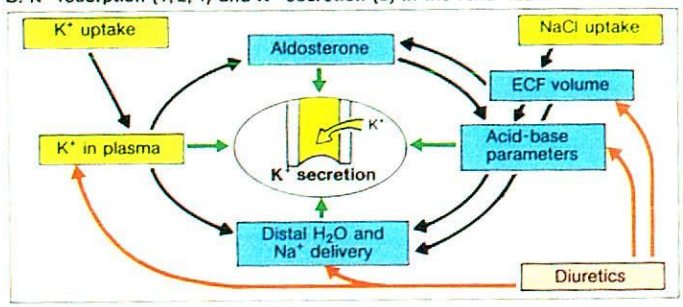
H^+ excretion as $H_2PO_4^-$ (titratable acid)



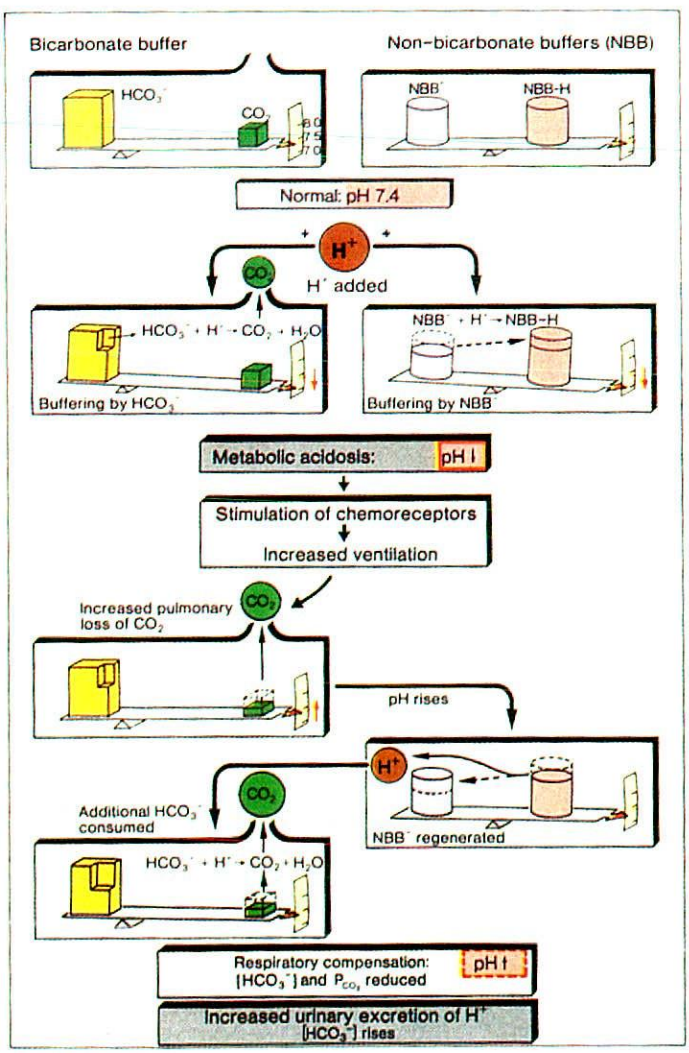
Resorption, secretion and excretion of K+



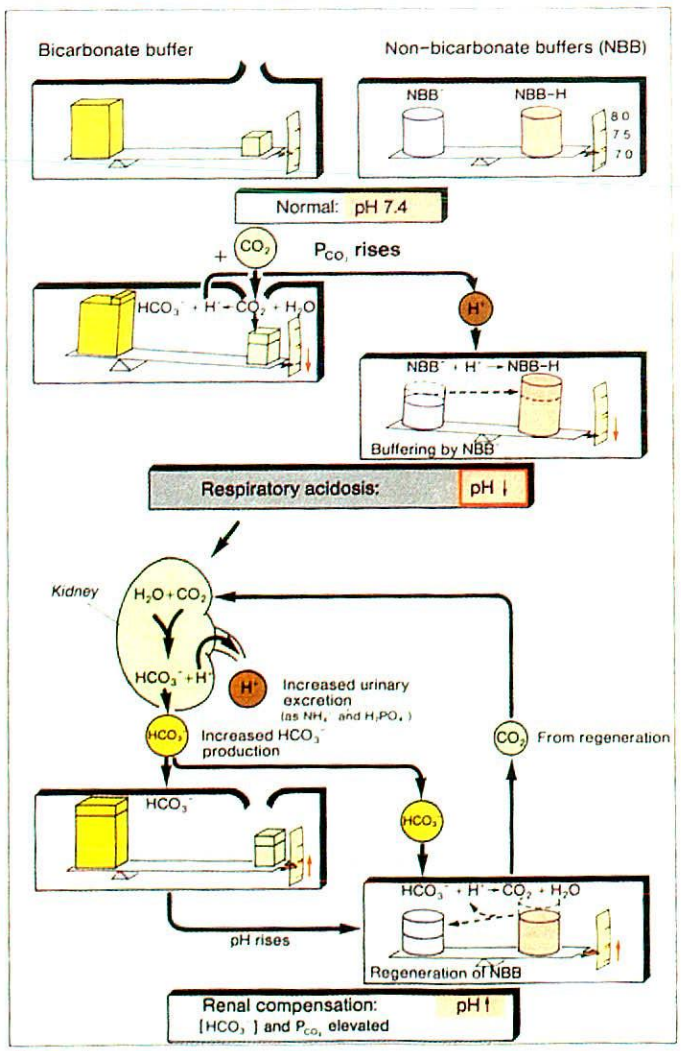
B. K+ resorption (1, 2, 4) and K+ secretion (3) in the renal tubule



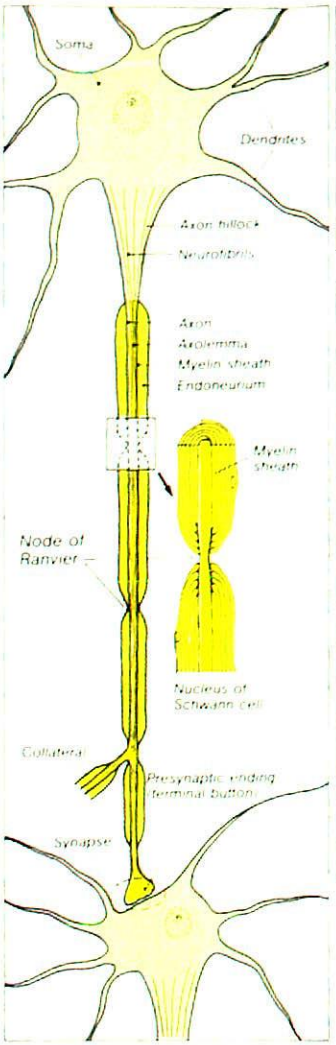
Influences on K+ secretion and excretion



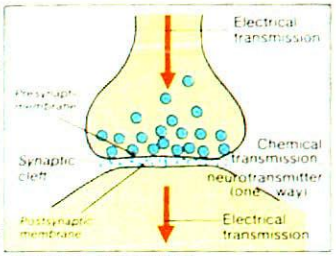
Metabolic acidosis



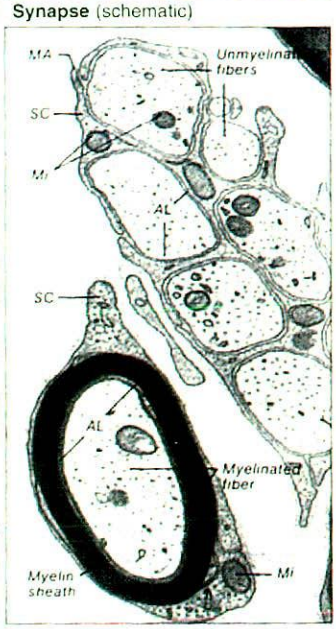
Respiratory



Neuron and synapse (schematic)

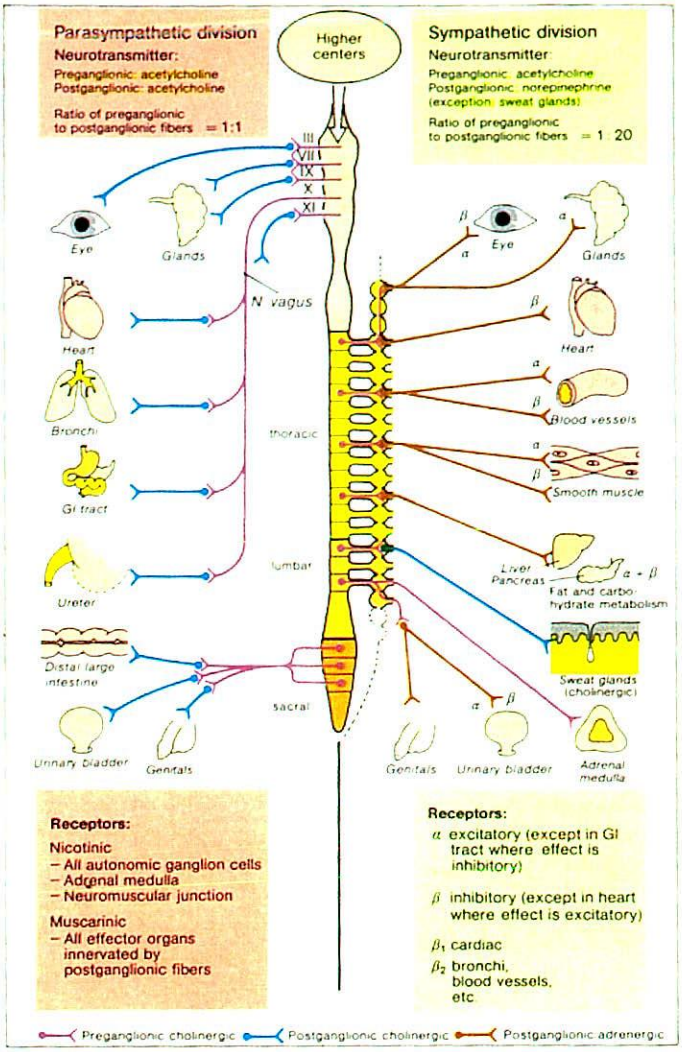


Synapse (schematic)

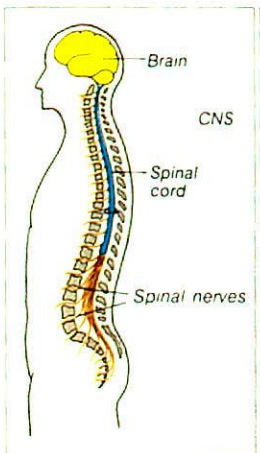


Myelinated and unmyelinated nerve fibers

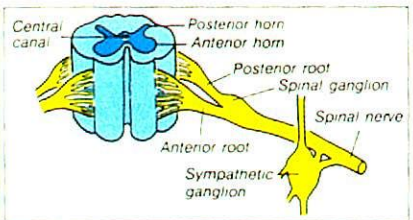
Electron microscopic section (Enlargement 1:22,000). SC-Schwann cell, AL - Axolemma, Mi-Mitochondria, MA-Mesaxon (-connection with extracellular space). The photograph was kindly placed at our disposal by Dr. Lauren A. Langford.



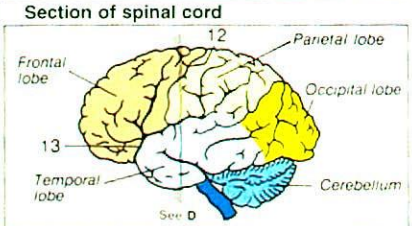
Survey of autonomic nervous system



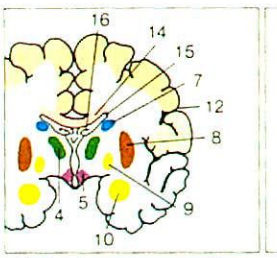
Central nervous system



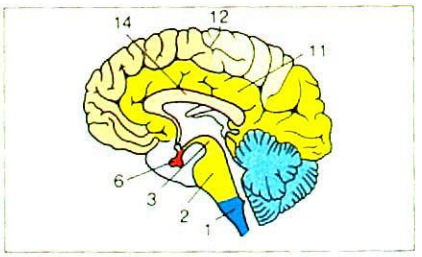
Section of spinal cord



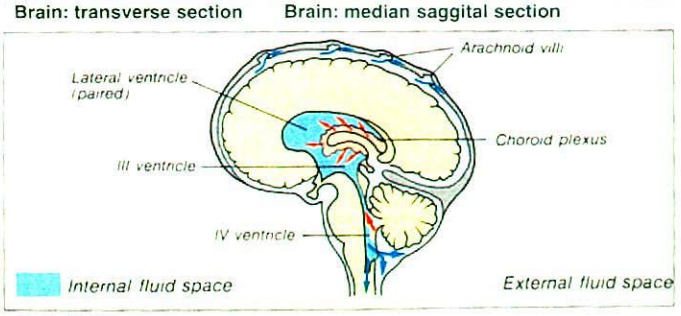
Brain: lateral surface



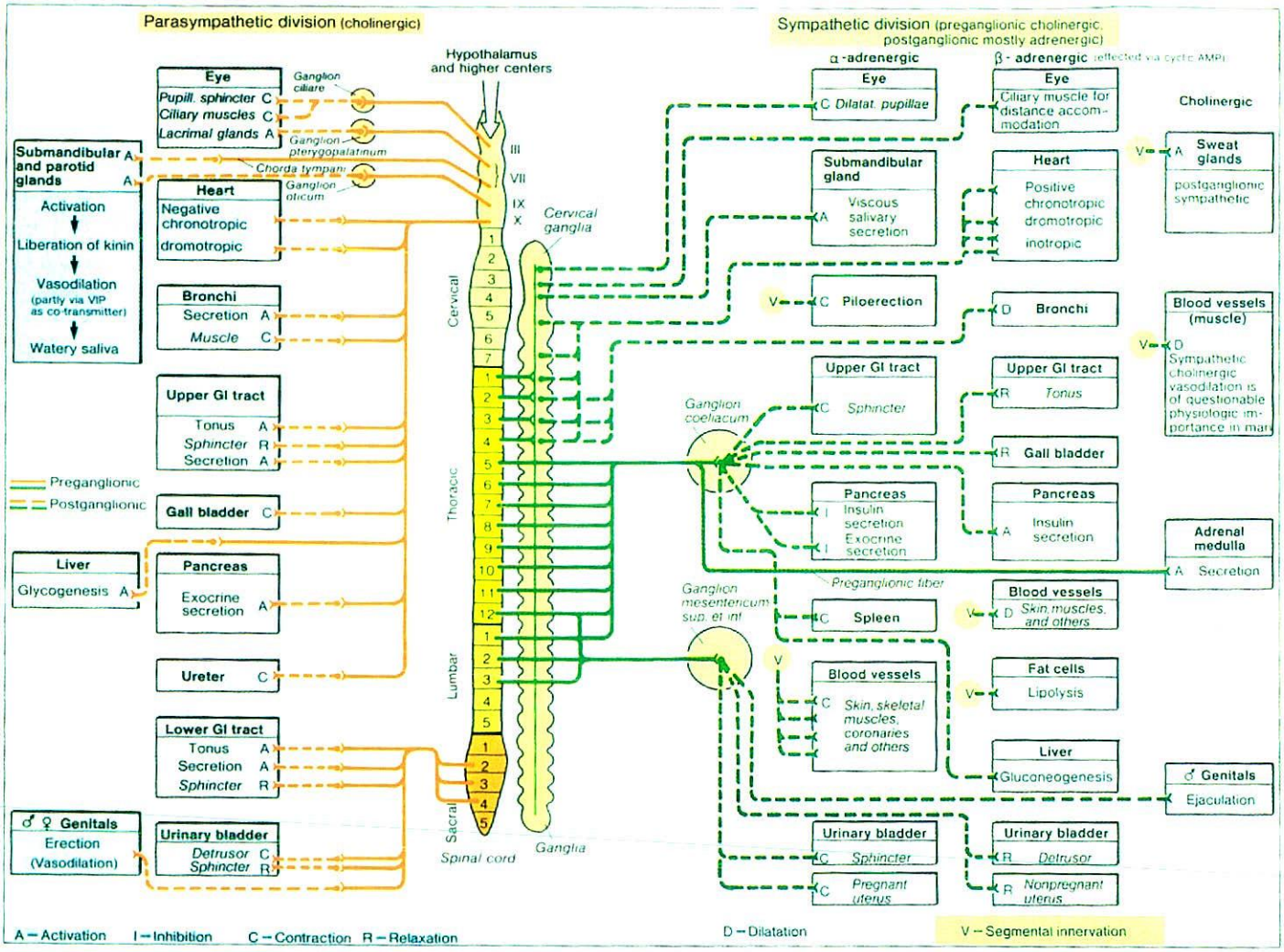
Brain: transverse section



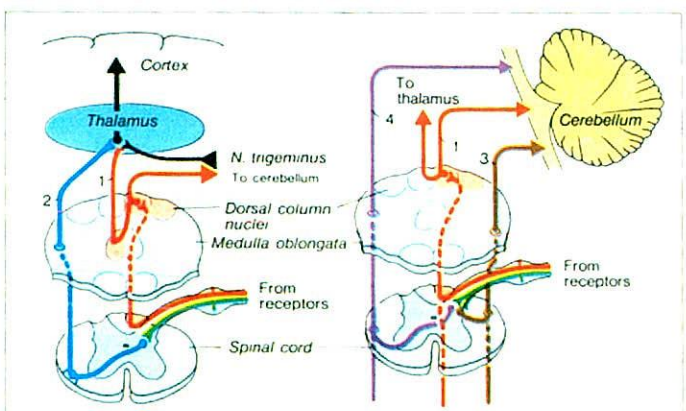
Brain: median saggital section



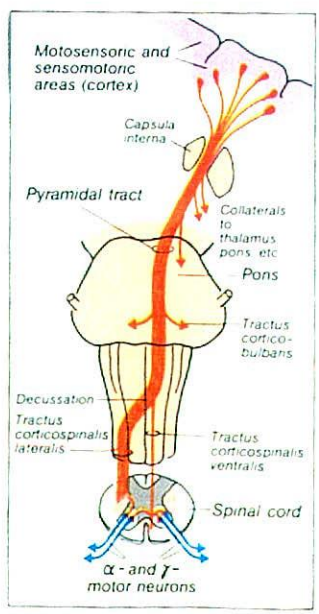
Brain: fluid spaces



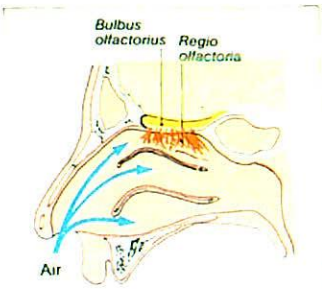
Functional organization of the autonomic nervous system



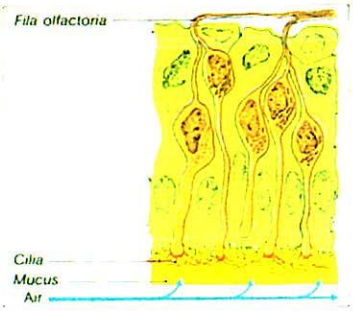
Spinal afferent pathways



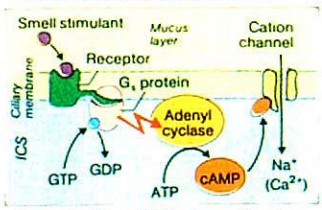
Pyramidal tract



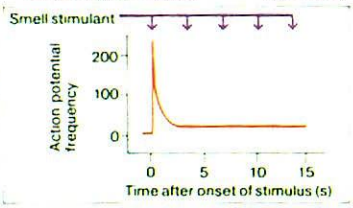
Nasal cavity: orgn of smell



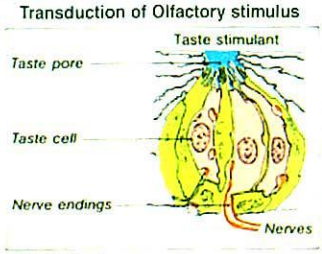
Olfactory epithelium (after Andres)



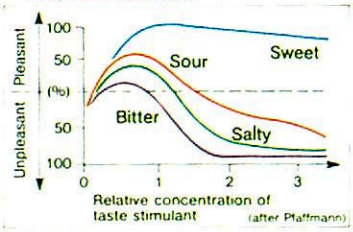
Transduction of Olfactory stimulus



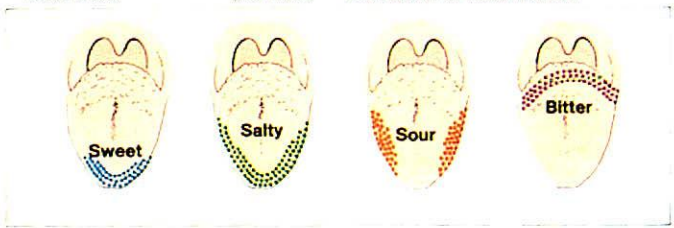
Adaptation to smell



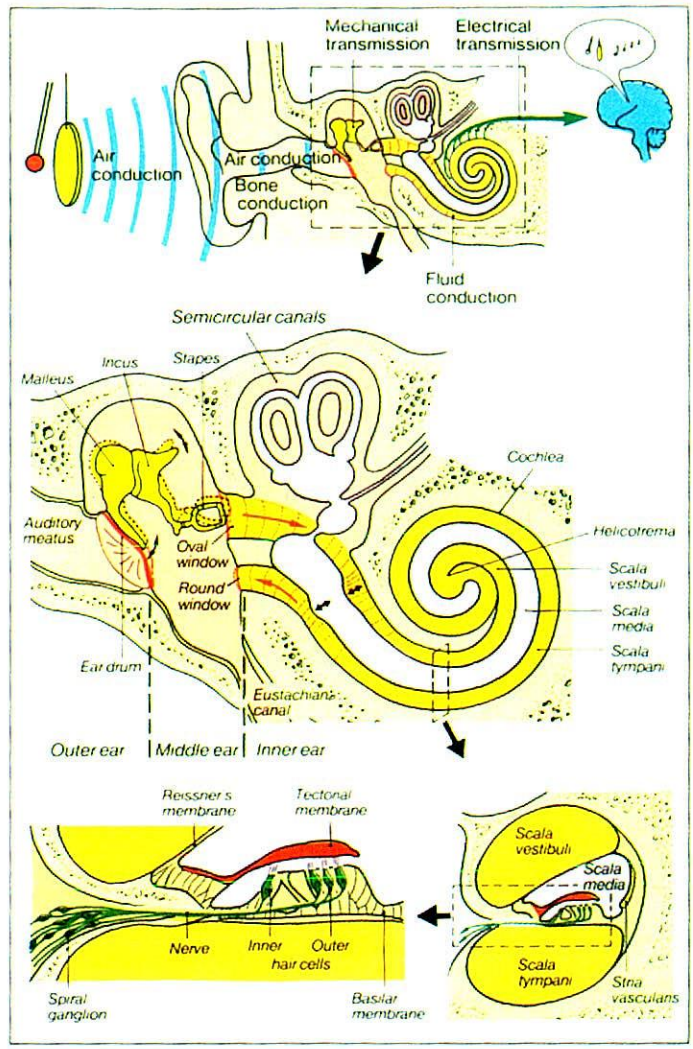
Taste buds (after Andres)



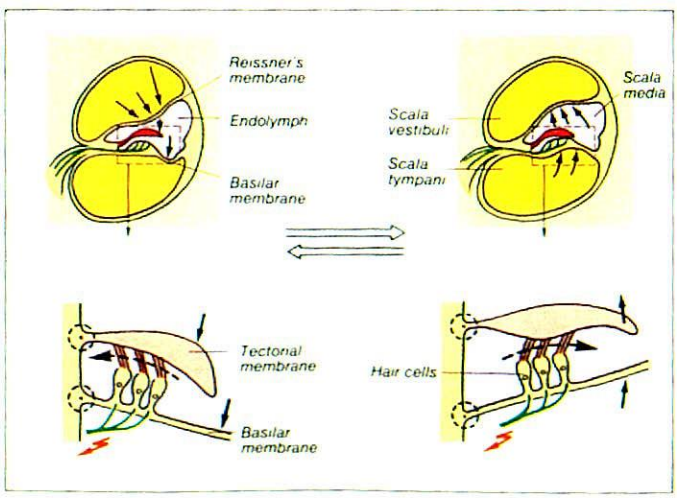
Evaluation of taste stimuli



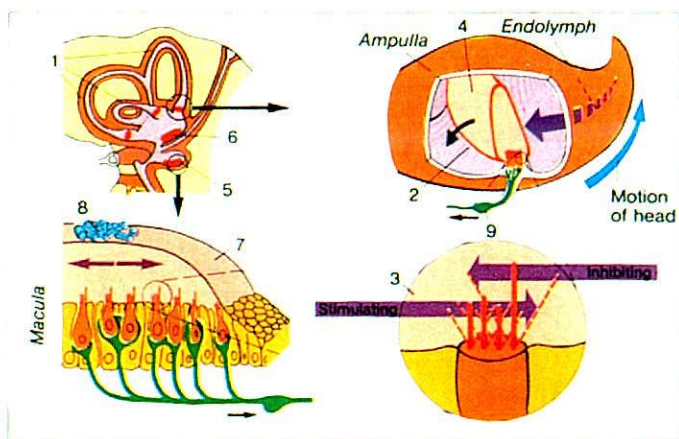
Localization of taste qualities on the tongue



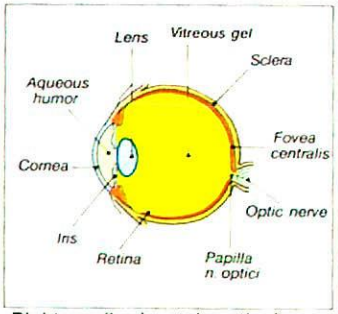
Sound transmission



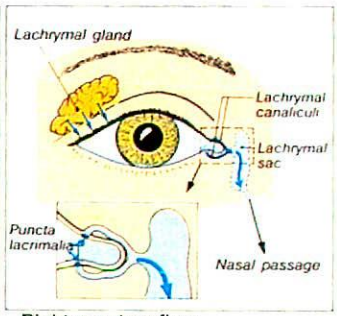
Excitation of hair cells by a shearing action on their hairs



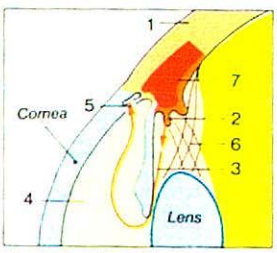
Vestibular organ



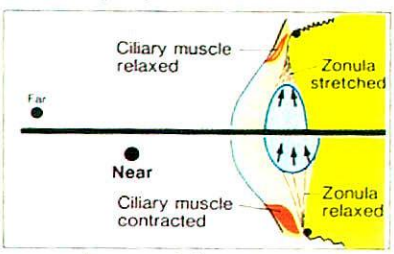
Right eye (horizontal section)



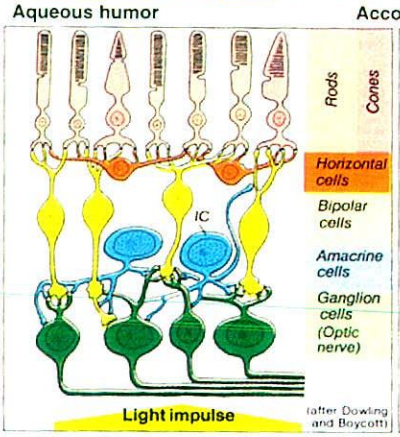
Right eye: tear flow



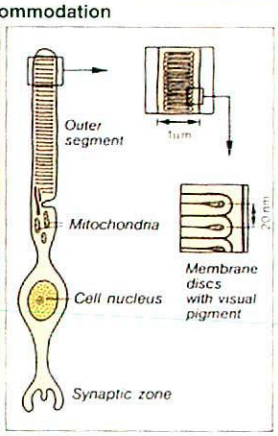
Aqueous humor



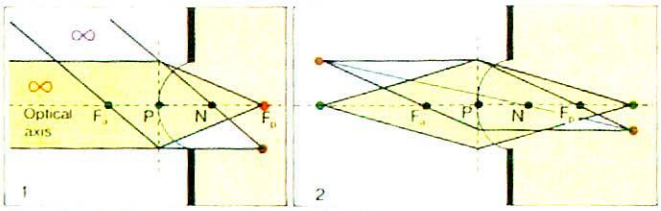
Accommodation



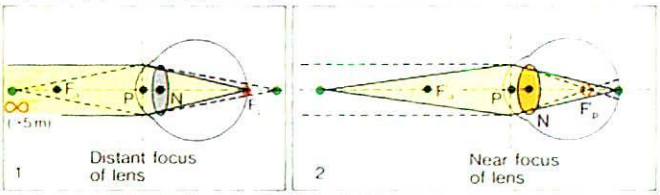
Retina (schematic)



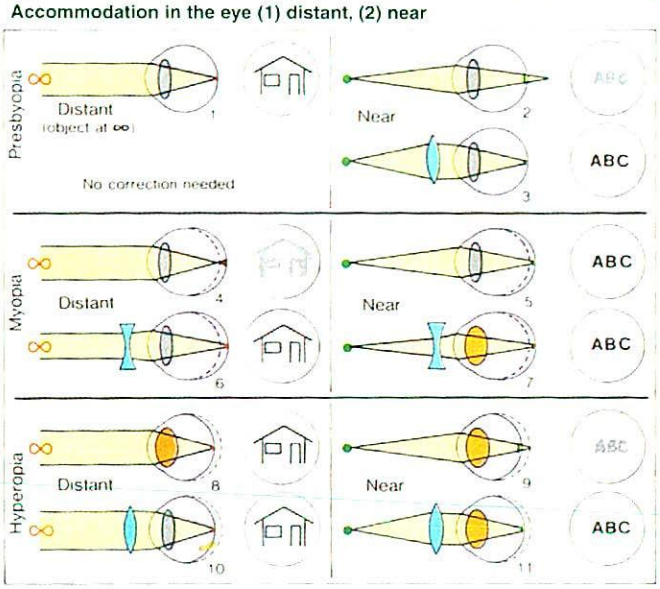
Rods



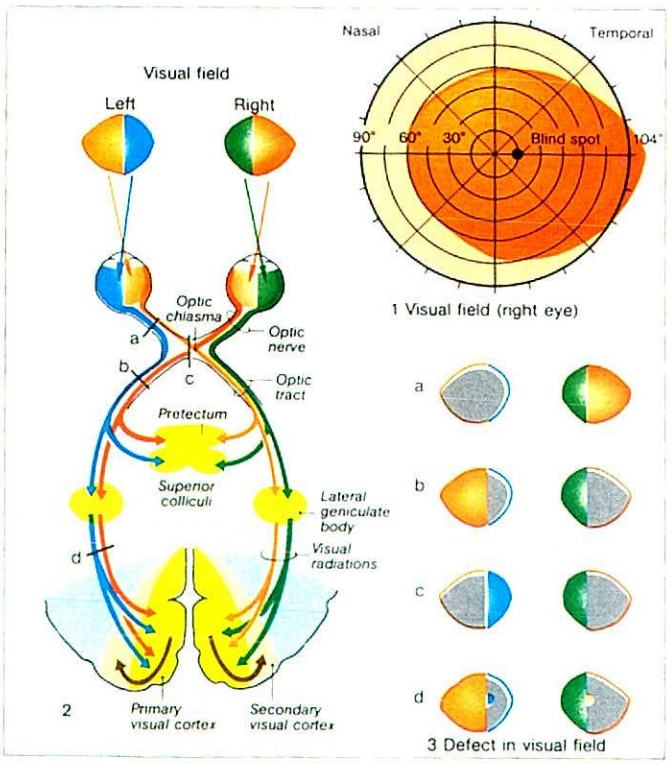
Optics: (1) distant, (2) near light source



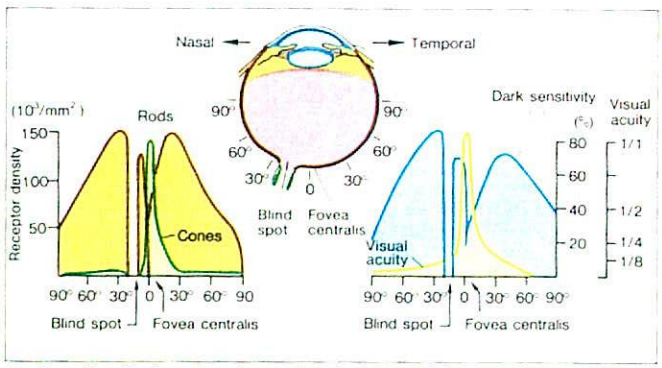
Accommodation in the eye (1) distant, (2) near



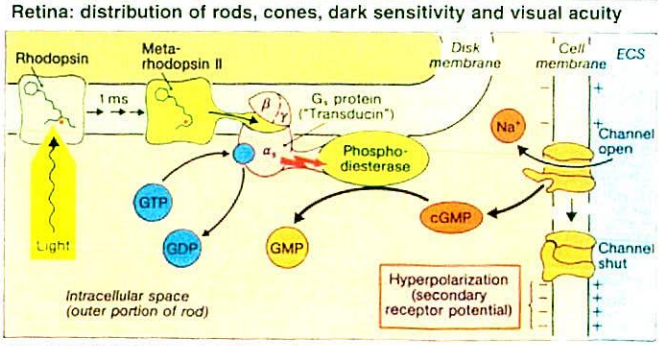
Visual defects



Visual pathway and field



Retina: distribution of rods, cones, dark sensitivity and visual acuity



Transduction process in the rods

1
General Physiology

General physiology

The goal of physiology is to explain the physical and chemical factors that are responsible for the origin, development and progression of life. Each type of life, from the very simple virus up to the largest tree or to the complicated human being, has its own functional characteristics.

Therefore, the vast of physiology can be divided into-

i. Viral physiology
ii. Bacterial physiology
iii. Celluar physiology
iv. Plant physiology
v Human physiology and many more subdivision.

(Ref. Guyton & Hall- 11th Edition; Page 3)

Human physiology

In *human physiology*, we attempt to explain the specific characteristics and mechanisms of human body that make it a living being. The very fact that we remain alive is almost beyond our own control, for hunger make us seek for food and fear makes us seek refuge. Sensations of cold make us provide warmth and other forces cause us to seek fellowship and to reproduce. Thus, the human being is actually an automaton, and the fact that we are sensing, feeling, and knowledgeable beings is part of this automatic sequence of life; these special attributes allow us to exit under widely varying conditions.

(Ref. Guyton & Hall- 11th Edition; Page 3)

In unicellular organisms, all vital processes occur in a single cell. As the evolution of multicellular organisms has progressed, various cell groups have taken over particular functions. In humans and other vertebrate animals, the specialized cell groups include - *a gastrointestinal system to* digest and absorb food, *a respiratory system* to take up O_2 and eliminate CO_2; *a urinary sytem* to remove wastes; *a cardiovascular system* to distribute food, O_2, and the products of metabolism; *a reproductive system* to perpetuate the species; and *nervous and endocrine systems* to coordinate and integrate the functions of the other systems. This book is concerned with the way these systems function and the way each contributes to the functions of the body as a whole.

This chapter presents general concepts and principles that are basic to the function of all the systems. It also includes a short review of fundamental aspects of cell physiology. Additional aspects of cellular and molecular biology are considered in the relevant chapters on the various organs.

Homeostatic mechenisms of the major functional systems

Homeostasis : The term *homeostsis* is used by the physiologist to mean maintenance of nearly constant conditions in the internal environment.

Essentially all organs and tissues of the body perform functions that help to maintain these constant conditions. For instant, the lungs provide oxygen to the extra cellular fluid to replinish the oxygen used by the cells, the kidneys maintain constant ionic concentrations and gastrointestinal system provides nutrients.

(Ref. Guyton & Hall- 11th Edition; Page 4)

The different functional systems of the body

1. ***Extracellular fluid transport and mixing system-*** *The blood circulatory system* : Extracellular fluid transported through all parts of the body in two stages. The first stage is movement of blood through the body in the blood vessels, and the second is movement of fluid between the blood capillaries and the intracellular spaces between the tissue cells.

   All the blood in the circulation traverses the entire circulatory circuit an average of once each minute when the body is at rest and as many as six times each minute when a person is extremely active.

   As blood passes through the blood capillaries continual exchange of extracellular fluid also occurs between the plasma portion of the blood and the interstitial fluid that fills the intercellular spaces. The walls of the capillaries are permeable to most molecules in the plasma of the blood, with the exception of the large plasma protein molecules. Therefore, large amounts of fluid and its dissolved constituents diffuse back and forth between the blood and the tissue spaces. This process of diffusion is caused by kinetic motion of the molecules in both the plasma and the interstitial fluid. That is, the fluid and dissolved molecules are continually moving and bouncing in all directions within the plasma and the fluid in the intercellular spaces, and also through the capillary pores. Few cells are located more than 50 micrometers from a capillary, which ensures diffusion of almost any substance from the capillary to the cell within a few seconds. Thus, the extracellular fluid everywhere in the body-both that of the plasma and that of the interstitial fluid-is continually being mixed, thereby maintaining almost complete homogeneity of the extracellular fluid throughout the body.

   (Ref. Guyton & Hall -11th Edition; Page 4)

2. ***Origin of nutrients in the extracellular fluid*** :
   a. *Respiratory system* : The blood picks up oxygen in the alveoli, thus acquiring the oxygen needed by he cells.
   b. *Gastrointestinal tract* : Here different dissolved nutrients, including carbohydrates, fatty acids, and amino acids, are absorbed from the ingested food into the extracellular fluid of the blood.
   c. *Liver and other organs* : The liver changes the chemical compositions of many of these substances to more usable forms, and other tissues of the body- fat cells, gastrointestinal mucosa, kidneys, and endocrine glands- help modify the absorbed substances or store them until they are needed.
   d. *Musculoskeletal system* : The musculoskeletal system provide the body to move to the appropriate place at the appropriate time to obtain the foods for nutrition. It also provides motility for protection against adverse surroundings, without which the entire body, along with its homeostatic mechanisms, could be destroyed instantaneously.

   (Ref. Guyton & Hall -11th Edition; Page 5)

3. ***Removal of metabolic end products*** :
   a. Removal of carbon dioxide by the lungs. Carbon dioxide is the most abundant of all the end products of metabolism.
   b. *Kidneys* removes most of the other substances from plasma include different end products of cellular metabolism, such as urea and uric acid; they also include excesses of ions and water from the food that might have accumulated in the extra cellular fluid.

   (Ref. Guyton & Hall -11th Edition; Page 5)

4. ***Regulation of body function*** :

   Body function is regulated by two major regulatory system.

   A. ***Nervous regulation*** : The nervous system is composed of three major parts - the sensory input portion, the central nervous system (or integrative portion) and the motor portion.
      a. *Sensory receptors :* Detect the state of the body or the state of surroundings such as touches, visual image etc.
      b. *Nervous system :* Composed of brain and spinal cord. The brain can store information, general thoughts, create ambition and determine reactions that the body performs in response to the sensations.
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   A large segment of the nervous system is called the *autonomic system*. It operates at a subconscious level and controls many functions of the internal organs, including-
   i. The level of pumping activity by the heart.
   ij. Movements of the gastrointestinal tract
   iii. Secretion by many of the bodys glands.

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   B. ***Hormonal system of regulation:*** Located in the body are eight major endocrine glands that secrete chemical substances, called *hormones*.

   Hormones are transported in the extracellular fluid to all parts of the body to help regulation of cellular function, such as -
   1. Thyroid hormone : Increases the rate of most chemical reactions in all cells thus helping to set the tempo of bodily activity.
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   Thus, the hormones are a systems of regulation that complements the nervous system.

The nervous system in general, regulates many muscular and secretory activities of the body, where as the hormonal system regulates mainly the metabolic functions.

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Hundreds of control systems working for maintenance of homeostasis show two common modes of actions -

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Essentially all control system of the body operate by negative feed back system.

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Positive feedback can sometimes be useful- explain.

In rare instances, the body has learned to use positive feedback to its advantage as follows :

1. *Blood clotting* : When a blood vessel is ruptured a clot begins to form. Multiple enzymes called clotting factors are activated with the clot itself. Some of these factors activates the other inactivated enzyme and causing still more clot.
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3. *Generation of nerve signals* : When the membrane of a nerve fibre is stimulated, this causes slight leakage of sodium ions through sodium channels in the nerve membrane to the interior of the fibre. The sodium ions entering the fibre then change the membrane potential, which in turn causes more opening of the channels, more change of potential, still more opening of channels and so forth. Thus creates the nerve action potential which excites the nerve fibre still further along its length and ultimately signals goes all the way to all ends of the nerve fiber.

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Q. 00. **How does the cell membrane contribute to cell homeo stasis.**

Ans. Role of the cell membrane in cell homeostasis :

a. *Role of the cell membrane lipid in cell homeostasis* :

i. The lipid layer in the middle of the membrane is impermeable to the usual water-soluble substances, such as ions, glucose, and urea. Fat-soluble substances, such as oxygen, carbon dioxide, alcohol, can penetrate this portion of the membrane with ease.

ii. The cholesterol in the cell membrane mainly help to determine the degree of permeability of the bilayer to water soluble constituents of the body fluids. The cholesterol also controls much of the fluidity of the membrane as well.

(Ref. Guyton. 11th Edition; Page-13)

b. *Role of the cell membrane proteins in cell homeostasis* :

i. *Adhesion molecules* : Some are cell *adhesion molecules* that anchors cells to their neighbors or to basal lamina.

ii. *Pumps* : There are proteins that function as *pumps*, actively transporting ions across the membrane.

iii. *Carriers* : Some proteins function as *carriers*, transporting substances down electrochemical gradient by facilitated diffusion.

iv. *Ions chennels* : Still others are *ions chennels*, which, when activated, permit the passage of ions into or out of the cell.

v. *Receptors* : Proteins in another group function as *receptors* that bind neurotransmitters and hormones, initiating physiological changes inside the cell.

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C. *Role of the cell membrane cabohydrate in cell homeostasis* :

i. Many of them are electrically negatively charged, which gives most cells an over all negatively surface charge that repels other negative objects.

ii. The glycocalyx of some cells attaches to the glycocalyx of other cells, thus attaching cell one to another.

iii. Many of the carbohydrates act as receptor substances for binding hormones such as insulin, and when bound, this combination activates attached internal proteins that in turn activate a cascade of intercellular enzymes.

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Normal ranges and physical characteristics of important extracellular fluid constituents : *Table-1* lists the more important constituents and physical characteristics of extracellular fluid along with their normal values, normal range and maximum limits without causing death for short periods of time. Note specially the narrowness of the normal range for each one of these values out side these ranges are usually the cause of or the result of illness.

Even for more important are the limits beyond which abnormalities can cause death. For instance-

i. An increase in the body temperature of only 11°F (7°C) above normal can often lead to vicious circle of increasing cellular metabolism that literally destroys the cells.

ii. Very narrow range for the acid base balance of the body, with a normal pH value of 7.4 and lethal values only about 0.5 on either side of the normal value.

iii. Another especially important factor is potassium ion, for whenever its concentration falls to less than one third normal, the person is likely to be paralyzed because of inability of the nerves to carry nerve signals, and if ever it rises to two or more times normal, the heart muscle is likely to be depressed severely.

iv. Also when the calcium ion concentration falls below about one half normal the person is likely to experience tetanic contraction of muscles throughout the body because of spontaneous generation of nerve impulses in the peripheral nerves.

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Thus, consideration of these example should give one an extreme appreciation of the value and even in necessity of the vast numbers of control systems that keep the body operating in health; in absence of any one of thease controls serious illness or death can result. *(Ref. Guyton & Hall- 11th Edition; Page 7)*

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Constituents	*Normal value*	*Normal range*	*Approximate Non lethal limits*	*Units*
Oxygen	40	35 - 45	10 - 1000	mm Hg
Carbon dioxide	40	35 - 45	5 - 80	mm Hg
Sodium	142	138 - 146	115 - 175	mmol/L
Potassium	4.2	3.8 - 5.0	1.5 - 9.0	mmol/L
Calcium ion	1.2	1.0 - 1.4	0.5 - 2.0	mmol/L
Chloride ion	108	103 - 112	70 - 130	mmol/L
Bicarbonate ion	28	24 - 32	8 - 45	mmol/L
Glucose	85	75 - 95	20 - 1500	mg/dl
Body temperature	98.4 (37.0)	98 - 98.8(37.0)	65 - 110(18.3-43.3)	°F(°C)
Acid-base	7.4	7.3 - 7.5	6.9 - 8.0	pH

1
General Physiology

General physiology

The goal of physiology is to explain the physical and chemical factors that are responsible for the origin, development and progression of life. Each type of life, from the very simple virus up to the largest tree or to the complicated human being, has its own functional characteristics.

Therefore, the vast of physiology can be divided into-

i. Viral physiology
ii. Bacterial physiology
iii. Celluar physiology
iv. Plant physiology
v Human physiology and many more subdivision.

(Ref. Guyton & Hall- 11th Edition; Page 3)

Human physiology

In *human physiology*, we attempt to explain the specific characteristics and mechanisms of human body that make it a living being. The very fact that we remain alive is almost beyond our own control, for hunger make us seek for food and fear makes us seek refuge. Sensations of cold make us provide warmth and other forces cause us to seek fellowship and to reproduce. Thus, the human being is actually an automaton, and the fact that we are sensing, feeling, and knowledgeable beings is part of this automatic sequence of life; these special attributes allow us to exit under widely varying conditions.

(Ref. Guyton & Hall- 11th Edition; Page 3)

In unicellular organisms, all vital processes occur in a single cell. As the evolution of multicellular organisms has progressed, various cell groups have taken over particular functions. In humans and other vertebrate animals, the specialized cell groups include - *a gastrointestinal system to* digest and absorb food, *a respiratory system* to take up O_2 and eliminate CO_2; *a urinary sytem* to remove wastes; *a cardiovascular system* to distribute food, O_2, and the products of metabolism; *a reproductive system* to perpetuate the species; and *nervous and endocrine systems* to coordinate and integrate the functions of the other systems. This book is concerned with the way these systems function and the way each contributes to the functions of the body as a whole.

This chapter presents general concepts and principles that are basic to the function of all the systems. It also includes a short review of fundamental aspects of cell physiology. Additional aspects of cellular and molecular biology are considered in the relevant chapters on the various organs.

Homeostatic mechenisms of the major functional systems

Homeostasis : The term *homeostsis* is used by the physiologist to mean maintenance of nearly constant conditions in the internal environment.

Essentially all organs and tissues of the body perform functions that help to maintain these constant conditions. For instant, the lungs provide oxygen to the extra cellular fluid to replinish the oxygen used by the cells, the kidneys maintain constant ionic concentrations and gastrointestinal system provides nutrients.

(Ref. Guyton & Hall- 11th Edition; Page 4)

The different functional systems of the body

1. ***Extracellular fluid transport and mixing system***- *The blood circulatory system* : Extracellular fluid transported through all parts of the body in two stages. The first stage is movement of blood through the body in the blood vessels, and the second is movement of fluid between the blood capillaries and the intracellular spaces between the tissue cells.

   All the blood in the circulation traverses the entire circulatory circuit an average of once each minute when the body is at rest and as many as six times each minute when a person is extremely active.

   As blood passes through the blood capillaries continual exchange of extracellular fluid also occurs between the plasma portion of the blood and the interstitial fluid that fills the intercellular spaces. The walls of the capillaries are permeable to most molecules in the plasma of the blood, with the exception of the large plasma protein molecules. Therefore, large amounts of fluid and its dissolved constituents diffuse back and forth between the blood and the tissue spaces. This process of diffusion is caused by kinetic motion of the molecules in both the plasma and the interstitial fluid. That is, the fluid and dissolved molecules are continually moving and bouncing in all directions within the plasma and the fluid in the intercellular spaces, and also through the capillary pores. Few cells are located more than 50 micrometers from a capillary, which ensures diffusion of almost any substance from the capillary to the cell within a few seconds. Thus, the extracellular fluid everywhere in the body-both that of the plasma and that of the interstitial fluid-is continually being mixed, thereby maintaining almost complete homogeneity of the extracellular fluid throughout the body.

   (Ref. Guyton & Hall -11th Edition; Page 4)

2. ***Origin of nutrients in the extracellular fluid*** :
   a. *Respiratory system* : The blood picks up oxygen in the alveoli, thus acquiring the oxygen needed by he cells.
   b. *Gastrointestinal tract* : Here different dissolved nutrients, including carbohydrates, fatty acids, and amino acids, are absorbed from the ingested food into the extracellular fluid of the blood.
   c. *Liver and other organs* : The liver changes the chemical compositions of many of these substances to more usable forms, and other tissues of the body- fat cells, gastrointestinal mucosa, kidneys, and endocrine glands- help modify the absorbed substances or store them until they are needed.
   d. *Musculoskeletal system* : The musculoskeletal system provide the body to move to the appropriate place at the appropriate time to obtain the foods for nutrition. It also provides motility for protection against adverse surroundings, without which the entire body, along with its homeostatic mechanisms, could be destroyed instantaneously.

   (Ref. Guyton & Hall -11th Edition; Page 5)

3. ***Removal of metabolic end products*** :
   a. Removal of carbon dioxide by the lungs. Carbon dioxide is the most abundant of all the end products of metabolism.
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Acid-base	7.4	7.3 - 7.5	6.9 - 8.0	pH

Chemical compositions of extracellular and intracellular fluids :

	Extracellular fluid	*Intracellular fluid*
Na^+	142 mEq/L	10 mEq/L
K^+	4 mEq/L	140 mEq/L
Ca^{++}	*2.4 mEq/L*	*0.0001 mEq/L*
Mg^{++}	*1.2 mEq/L*	*58 mEq/L*
Cl^-	103 mEq/L	4 mEq/L
HCO_3^-	28 mEq/L	10 mEq/L
Phosphates	*4 mEq/L*	*75 mEq/L*
SO_4^{--}	*1 mEq/L*	*2 mEq/L*
Glucose	90 mg/dl	0 to 20 mg/dl
Amino acids	30 mg/dl	200 mg/dl?
Cholesterol		
Phospholipids	*0.5 gm/dl*	*2 to 95 gm/dl*
Neutral fat		
PO_2	35 mm of Hg	20 mm of Hg?
PCO_2	*46 mm of Hg*	*50 mm of Hg?*
pH	*7.4*	*7.0*
Proteins	2 gm/dl (5 mEq/L)	16 gm/dl (40 mEq/L)

(Ref. Guyton & Hall- 11th Edition; Page-46)

Osmolar substances in plasma, extracellular fluid (ECF) and intracellular fluid (ICF) *in mosm/liter*

	Plasma (mosm/liter of H_2O)	*Interstitial (mosm/liter of H_2O)*	*Intracellular (mosm/liter of H_2O)*
Na^+	*142*	139	14
K^+	4.2	4	*140*
Ca^{++}	1.3	1.2	**0**
Mg^+	0.8	0.7	20
Cl^-	*108*	108	4
HCO_3	24	28.3	10
HPO_4^- /$H_2PO_4^-$	2	2	*11*
SO_4^-	0. 5	0.5	1
Phosphocreatine	-	-	45
Carnosine	-	-	14
Amino acids	2	2	8
Creatine	0.2	0.2	9
Lactate	1.2	1.2	1.5
Adenosine triphosphate	-	-	5
Hexose monophosphate	-	-	3.7
Glucose	5.6	5.6	-
Protein	1.2	0.2	4
Urea	4	4	4
Others	4.8	3.9	10
Total mOsm/liter	301.8	300.8	301.2
Corrected osmolar activity (mOsm/liter)	282.0	281.0	281.0
Total osmotic pressure at 37°C (mm Hg).	*5443*	*5423*	*5423*

(Ref. Guyton & Hall- 11th Edition; Page 294)

Automaticity of the body

Purpose :

1. The overall organization of the body.
2. The means by which the different parts of the body operate in harmony.

Body is actually a social order of about ***100 trillion cells*** organized into different functional structures, some of which are called organs. Each functional structure provides its share in the maintenance of homeostatic conditions in the extracellular fluid, which is called the internal environment. As long as normal conditions are maintained in the internal environment, the cells of the body continue to live & function properly. Thus each cell benefits from homeostasis, and in turn, each cell contributes its share toward the maintenance of homeostasis. The reciprocal interplay provides continuous automaticity of the body until one or more functional systems lose their ability to contribute their share of function. When this happens, all the cells of the body suffer. Extreme dysfunction leads to death, where as moderate dysfunction leads to sickness.

(Ref. Guyton & Hall -11th Edition; Page 9)

Organization of the body

The cells that make up the bodies of all but the simplest multicellular animals, both aquatic and terrestrial, exist in an " internal sea" of extracellular fluid (***ECF***) enclosed within the integument of the animal. From this fluid, the cells take up O_2 and nutrients; into it, they discharge metabolic waste products. The ECF is more dilute than present day seawater, but its composition closely resembles that of the primordial oceans in which, presumably, all life originated.

In animals with a closed vascular system, the *ECF* is divided into 2 components :

1. *Interstitial fluid*
2. *Circulating blood plasma.*

The plasma and the cellular elements of the blood, principally red blood cells, fill the vascular system, and together they constitute the *total blood volume*. The interstital fluid is that part of the ECF that is outside the vascular system, bathing the cells. About one third of the *total body water (TBW)* is extracellular; the remaining two thirds are intracellular *(intracellular fluid)*.

(Ref. W. F. Ganong 22th Edition; Page-1)

Content in grams of A 70 kilogram man :

Constituent	Amount (grams)
1. Water	41,400 (41.4 kg)
2. Fat	12,600 (12.6 kg)
3. Protein	12,600 (12.6 kg)
4. Carbohydrate	300
5. Na	63
6. K	150
7. Ca	1,160
8. Mg	21
9. Cl	85
10. P	670
11. S	112
12. Fe	3
13. I	0.014

(Ref. Guyton & Hall- 11th Edition; Page 878)

Body composition

In the average 70 kilogram adult male :

Constituent	% of total body weight
1. Protein & related substances	: 18%
2. Mineral	: 7%
3. Fat	: 15%
4. Water (42 litre or)	: 60%

a. *Intracellular component* of body water (28 litres or) : 40%

b. *Extracellualr component* of body water (14 litres) : 20%

i. 25% of the extracellular component is in the vascular system-(*plasma*-3 litres) : 05%

ii. 75% of the extracellular component is in the outside of blood vessels (*Interstitial fluid*) : 15%

(Total blood volume is about 8% of body weight.)

(Ref. W. F. Ganong 22th Edition; Page 1)

iii. *Transcellular fluid : 1 to 2 litres*

This compartment includies- fluid in the synovial, peritonial, pericardial, and intraoccular spaces, as well as the cerebrospinal fluid.

(Ref. Guyton & Hall- 11th Edition; Page-292)

N.B. In the average 70-kilogram adult human, the total body water is about 60% of the body weight, or about 42 liters. This percentage can change, depending on age, sex, and degree of obesity. As a person grows older, the percentage of total body weight that is fluid gradually decreases. This is due in part to the fact that aging is usually associaed with an increased percentage of the body weight that is fat, which in turn decreases the percentage of water in the body. Because women normally have more body fat than men, they contain slightly less water than men in proportion to their body weight. Therefore when discussing the 'average' body fluid compartments, we should realize that variations exits, depending on age, sex, and percentage of body fat.

(Ref. Guyton & Hall- 11th Edition; Page-292)

Body fluid compartments

The body fluid is mainly distributed between two compartments

1. *Intracellular fluid compartment :* It is the sumtotal of the fluid content of all cells of the body. It is about 28 liters.
2. *Extracellular fluid compartment :* It is the fluid out side of the cell. It is about 14 litres.

   The extracellular fluid in turn is divided into the *interstitial fluid* and blood *plasma.*
3. There is another small compartment of fluid that is referred to as ***transcellular fluid.*** It is usually considered to be a specialized type of extracellular fluid, although in some cases, its composition may differ markedly from that of plasma or interstitial fluid. It constitutes about 1 to 2 liters.This compartments includes fluids-
   i. Synovial fluid
   ii. Peritonial fluid
   iii. Pericardial fluid
   iv. Intraocular fluid
   v. Cerebrospinal fluid.

(Ref. Guyton & Hall- 11th Edition; Page 292, 293)

% of total body fluid compartments :

Total body water (42 litre or) : 60%

a. *Intracellular component* of body water (28 litres or) : 40%

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(Ref. Guyton 11th Edition; Page 292)

The cell & its function

Organisation of cells :

The cell is the structural and functional unit of the living organism. Each of the 100 trillion or more cells in a human being is a living structure that can survive indefinitely and, in

most instances, can even reproduce itself provided its surrounding fluids contain appropriate nutrients.

A ***typical cell*** has two major parts- the *nucleus* and the *cytoplasm*. The nucleus is separated from the cytoplasm by a *nuclear membrane*, and the cytoplasm is separated from the surrounding fluid by a *cell membrane*, also called *plasma membrane*.

(Ref. Guyton & Hall- 11th Edition; Page 11, 12)

Physical structure of cell

The cell is not merely a bag of fluid, enzymes, and chemicals; it also contains highly organized physical structures, called *intracellular organelles*. *Structures of cell are followings* :

A. Cell membrane
B. Protoplasm
   a. **Nucleus**
      i. Nuclear membrane
      ii. Nucleolus
      iii. Nucleoplasm or nuclear sap
      iv. Chromatin
         1. Heterochromatin
         2. Euchromatin
   b. **Cytoplasm**
      i. ***Organelles***
         1. *Membranous organelles*
            Mitocondria
            Endoplasmic reticulumn
            Golgi complex
            Lysosomes
            Peroxisomes
         2. *Non membranous organelles*
            Ribosomes
            Centrioles
            Filaments
               Microfilaments
               Intermediate filaments
            Microtubules
      ii. ***Inclusions***
         1. Secretory granules
         2. Pigment granules
         3. Lipid and glycogen
         4. Crystals.

(Ref. Guyton & Hall- 11th Edition; Page12 & others)

The specialization of the cells in the various organs is very great, and no cell can be called 'typical' of all cells in the body. However a number of structures *(organelles)* are common to most cells.

(Ref. W. F. Ganong 22th Edition; Page 8)

Protoplasm

The different substances that make up the cell are collectively called protoplasm. Protoplasm is mainly composed of five basic substances- *water, electrolytes, proteins, lipids and carbohydrates.*

1. ***Water*** : The principal fluid medium of the cell is water, which is present in a concentration of between 70 to 85 percent. Many cellular chemicals are dissolved in water. Others are suspended in the water as solid particulates. Chemical reactions take place among the dissolved chemicals or at the surfaces of the suspended particles or membranes.

(Ref. Guyton & Hall- 11th Edition; Page 11)

2. ***Ions*** : The most

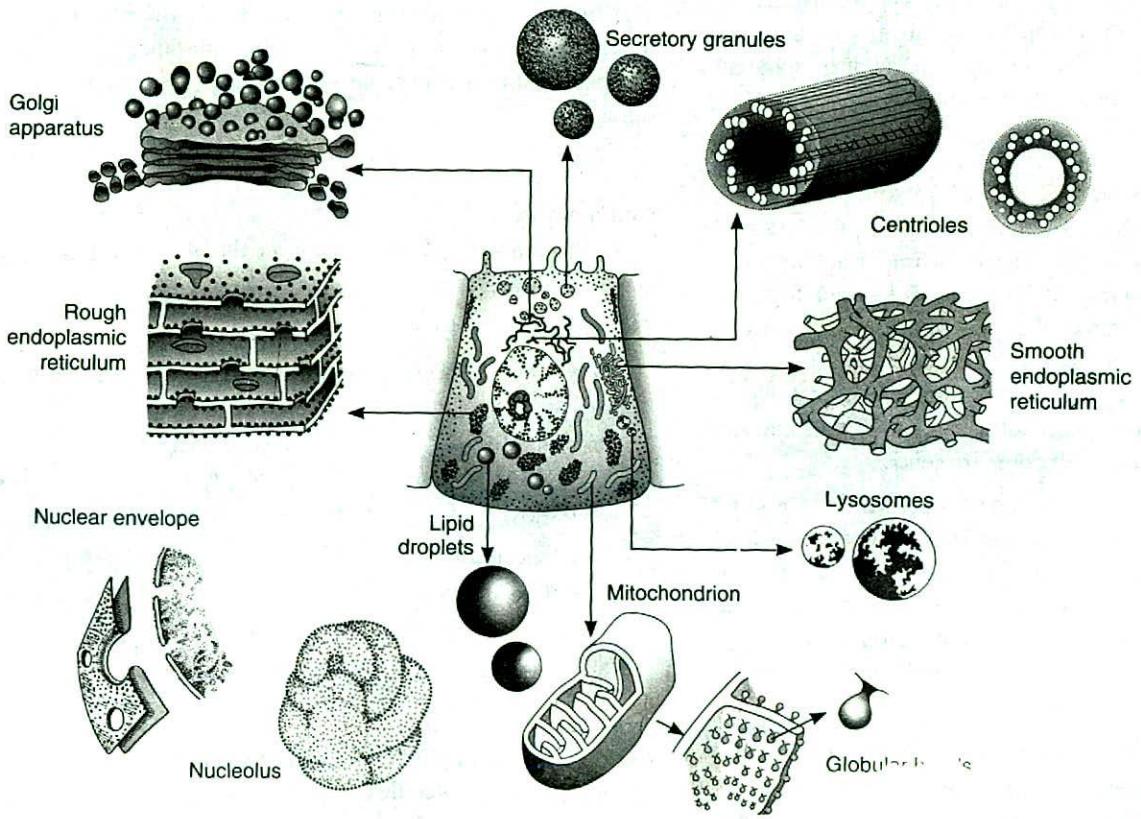


Fig: 1-1. Diagram showing a hypothetical cell in the center as shown with the light microscope. It is surrounded by various organelles.

important electrolytes in the cell are K^+, Mg^{++}, PO_4^{-3}, SO_4^{-2}, HCO_3^- and smaller quantities of Na^+, Ca^{++}, Cl^-.

Function :

i. Electrolytes provide inorganic chemicals for cellular reactions.

ii. They are necessary for operation of some of the cellular control mechenism. For instances, ions acting at the cell membrane are required for transmission of electro-chemical impulses in nerve and muscle fibres.

(Ref. Guyton & Hall- 11th Edition; Page 11)

3. ***Proteins*** : These normally constitute 10 to 20 percent of the cell mass.

These are of two types :

i. Structural proteins

ii. Functional proteins.

Structural proteins : They are polymers of many protein molecules, present in the cell mainly in the form of long thin filaments. The most prominent use of such intracellular filaments is to provide the contractile mechenism of all muscles. Filaments, however are also organised into microtubule that provide the *cyto-skeletons* of such organelles as cillia, nerve axons & the mitotic spindles of mitosing cells. Extracellularly fibrillar proteins are found specially in the collagen and elastin fibres of connective tissue, blood vessels, tendons, ligaments & so forth.

Globular proteins : Composed of individual protein molecules or at most, combination of a few molecules in a globular form rather than a fibrillar form. These are mainly enzymes of the cell & in contrast to the fibrillar proteins are often soluble in the cell fluid or integral parts of or adherent to membranous structures inside the cell.

(Ref. Guyton & Hall- 11th Edition; Page 11)

4. ***Lipids*** : Lipids are several types of substances that are grouped together because of their common properties of being soluble in fat solvents. The most important lipids in most cells are *phospholipids* and *cholesterol*, which together constitute about 2 per cent of the total cell mass. The special importance of phospholipids and cholesterol is that they are mainly insoluble in water and, therefore are used to form cell membrane as well as intra cellular membranous barriers that separate the different cell compartments.

In addition to phospholipids and *cholesterol*, some cells contains large quantities of *triglycerides*, also called *neutral fat*. In the so-called fat cells, triglycerides often account for as much as 95 per cent of the cell mass. The fat stored in this cells represents the body's main storehouse of energy-nutrient that can later be dissoluted and used for energy wherever in the body it is needed.

(Ref. Guyton & Hall- 11th Edition; Page 12)

5. ***Carbohydrates*** : Carbohydrates have little structural function in the cell except as part of glycoprotein molecules but they play a major role in nutrition of the cell. A small amount of carbohydrate is virtually always stored in the cells in the form of *glycogen* and can be used rapidly to supply the cells energy needs. Carbohydrate in the form of dissolved glucose is always present in the surrounding extracellular fluid, so that it is easily available to the cell. It is averaging 1% of total cell mass. As much as 3% in muscles & 6% in liver cells.

(Ref. Guyton & Hall- 11th Edition; Page 12)

Physical structure of the cell

The cell is not merely a bag of fluid, enzymes, and chemicals; it also contains highly organized physical structures, many of which are called *organelles*. The physical nature of each structure is equally as important to the function of the cell as the cell's chemical constituents. For instance, without one of the organelles, the *mitochondria,* more than 95 per cent of the cells energy supply would cease immeditely.

Membranous structures of the cell

Essentially almost all the organelles of the cell are lined by membranes. These membranes include-

1. Cell membrane
2. Nuclear membrane
3. Membrane of the endoplasmic reticulum.
4. Membrane of the mitochondria
5. Membrane of the lysosomes
6. Membrane of the Golgi apparatus.

The lipids of the membranes provide a barrier that prevents movements of water and water soluble substances from one cell compartment to the other because the water is not soluble in the lipids.

(Ref. Guyton & Hall- 11th Edition; Page 12)

Cell membrane

The cell membrane, which envelops the cell, is a thin, pliable, elastic structure.

Thickness : 7.5 to 10 nanometers.

Composition : It is composed almost entirely of proteins and lipids. The approximate composition is-

1. Protein			: 55%
2. Lipid		:	42%
a. Phospholipids	:	25%	
b. Cholesterol	:	13%	
c. Others lipids	:	4%	
5. Carbohydrates			: 3%

(Ref. Guyton & Hall- 11th Edition; Page 12)

Structure of cell membrane :

Its basic structure is a lipid bilayer interposed with large globular protein molecules.

a. *Lipid of the cell membrane* : Composed almost entirely of

phospholipids and cholesterol (lipid in nature). One part of the phospholipid and cholesterol is soluble in water, that is, *hydrophilic*, whereas the other part is soluble only in fat, that is, *hydrophobic*. The phosphate radicle of the phospholipid is hydrophilic and the fatty acid radicles are hydrophobic.

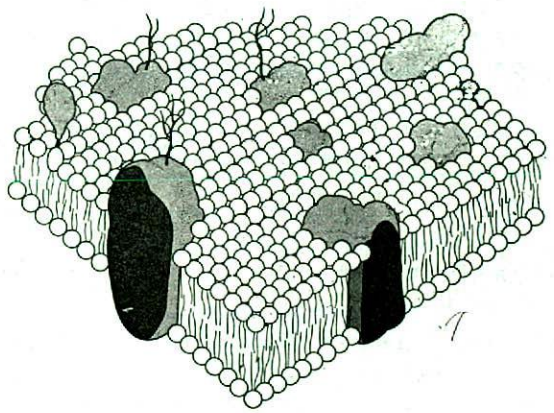


Fig: 1-2. Biological membrane. The phospholipid molecules each have two fatty acid chains (wavy lines) attached to a phosphate head (open circle). Proteins are shown as irregular coloured globules. Many are integral proteins, which extend through the membrane, but peripheral proteins are attached to the inside (not shown) and outside of the membrane, sometimes by glycosylphosphati -dylinositol (GPI) anchor.

The *lipid layer* in the middle of the membrane is impermeable to the usual water-soluble substances, such as ions, glucose, and urea. Conversely, fat-soluble substances, such as oxygen, carbon dioxide, alcohol, can penetrate this portion of the membrane with ease.

A special feature of the *lipid bilayer* is that it is a fluid and not a solid. Therefore, portions of the membrane can literally flow from one point to another along the surface of the membrane. Proteins or other substnces dissolved or floating in the lipid bilayer diffuse to all areas of the cell membrane.

The *cholesterol* in the cell membrane mainly help to determine the degree of permeability of the bilayer to water soluble constituents of the body fluids. The cholesterol also controls much of the fluidity of the membrane as well.

(Ref. Guyton & Hall- 11th Edition; Page 12, 13)

b. *The cell membrane proteins* : These are membrane proteins, most of which are glycoproteins. The cell membrane proteins are of two types :

i. *Integral proteins* : Many of the integral proteins provides structural *channels (or pores)* through which water soluble substances specially ions, can diffuse between the extracellular and intracellular fluid. These *protein channels* also have selective properties that allow preferential diffusion of some substances more than others.

Others of the integral proteins act as carrier proteins for transporting substances that otherwise could not penetrate the lipid bilayer. Some times these even transport substances in the direction opposite to their natural direction of diffusion, which is called *'active transport*. Still others acts as enzymes.

ii. *Peripheral proteins* : The peripherals proteins occur mainly on the inside of the membrane, and they offen are attached to one of the integral proteins. These peripheral proteins function almost entirely as enzymes or as other types of controllers of intracellular function.

(Ref. Guyton & Hall- 11th Edition; Page 13)

Functions of the membrane proteins :

1. Some are cell *adhesion molecules* that anchors cells to their neighbors or to basal lamina.
2. There are proteins that function as *pumps*, actively transporting ions across the membrane.
3. Some proteins function as *carriers*, transporting substances down electrochemical gradient by facilitated diffusion.
4. Still others are *ions chennels*, which, when activated, permit the passage of ions into or out of the cell.
5. Proteins in another group function as *receptors* that bind neurotransmitters and hormones, initiating physiological changes inside the cell.
6. Proteins also function as enzymes, catalyzing reactions at the surfaces of the membrane.
7. Some glycoproteins function in *antibody processing and distinguishing* self from nonself.

(Ref. Ganong 22th Edition; Page-9,10)

C. *Membrane carbohydrate* : Membrane carbohydrate occur almost invariably in combination with proteins or lipids in the form of glycoproteins or glycolipids. In fact most of the integral proteins are glycoproteins and about one tenth of the membrane lipid molecules are glycolipids. The 'glyco' portions of these molecules almost invariably protude to the outside of the cell, dangling outward from the cell surface. Many other carbohydrate compounds, called *proteoglycans*, which are mainly carbohydrate substances bound to small protein cores, often are loosely attached to the outer surface of the cell as well. Thus, the entire outside surface of the cell often has a loose carbohydrate coat called the *glycocalyx*.

The carbohydrate moieties attached to the outer surface of the cell have several important functions :

1. Many of them are electrically negatively charged, which gives most cells an over all negatively surface charge that repels other negative objects.
2. The glycocalyx of some cells attaches to the glycocalyx of other cells, thus attaching cell one to another.
3. Many of the carbohydrates act as receptor substances for binding hormones such as insulin, and when bound, this

combination activates attached internal proteins that in turn activate a cascade of intercellular enzymes.

4. Some carbohydrate moieties enter into immune reactions.

(Ref. Guyton & Hall- 11th Edition; Pages 14)

Membrane transport proteins

Membrane permeability & membrane transport proteins : Small, nonpolar molecules- including O_2 and N_2 and small uncharged polar molecules such as CO_2 diffuse across the lipid membranes of cells. However, the membranes have very limited permeability to other substances. Instead, they cross the membranes by endocytosis and exocytosis and by passage through highly specific ***transport proteins***, transmembrane proteins that form channels for ions or transport substances such as glucose, urea, and amino acids.

i. *Aquaporins* : The limited permeability applies even to water, with simple diffusion being supplemented throughout the body with various water channels (*aquaporins*).

ii. *Simple aqueous ion channels* : Some transport proteins are simple aqueous ion channels, though many of these have special features that make them effective for a given substance such as Ca^{++} or, in the case of aquaporins, for water.

iii. *Gated and continuously open channels* : Some of the transport proteins are continuously open and some are gated; ie, they have gates that open or close.

   a. *Voltage-gated* : Are gated by alterations in membrane potential. A typical voltage-gated channel is the Na^+ channel.

   b. *Ligand-gated* : Are opened or closed when they bind a ligand. A typical ligand-gated channel is the acetylcholine receptor.

   The ligand is often external, eg, a neurotransmitter or a hormone. However, it can also be internal; intracellular Ca^{++}, cAMP, lipids, or one of the G proteins produced in cells can bind directly to channels and activate them.

iv. *Mechanosensitive channels* : Some channels are also opened by mechanical stretch, and these mechanosensitive channels play an important role in cell movement.

v. *Carriers* : This transport proteins bind ions and other molecules and then change their configuration, moving the bound molecule from one side of the cell membrane to the other. Molecules move from areas of high concentration to areas of low concentration (down their *chemical gradient*), and cations move to negatively charged areas whereas anions move to positively charged areas (down their *electrical gradient*).

   Facilitated diffusion : When carrier proteins move substances in the direction of their chemical or electrical gradients, no energy input is required and the process is called facilitated diffusion. A typical example is glucose transport by the glucose transporter, which moves glucose down its concentration gradient from the ECF to the cytoplasm of cell.

   Active transport : This carriers transport substances against their electrical and chemical gradients. This form of transport requires energy and is called active transport. In animal cells, the energy is provided almost exclusively by hydrolysis of ATP. Not surprisingly, therefore, the carrier molecules are ATPases, enzymes that catalyze the hydrolysis of ATP. One of these ATPases is *sodium potassium-activated adenosine triphosphatase* (Na^+-K^+ ATPase), which is also known as the Na^+-K^+ pump. There are also H^+-K^+ ATPases in the gastric mucosa and the renal tubules. Ca^{++} ATPase pumps Ca^{++} out of cells. Proton ATPases acidify many intracellular organelles, including parts of the Golgi complex and lysosomes. F-ATPases are present in mitochondria and synthesize ATP. Some cell membranes contain ATPases that transport Ca^{++}.

vi. *Uniports* : Some of the transport proteins are called uniports, because they transport only one substance.

vii. *Symports* : Transport requires the binding of more than one substance to the transport protein and the substances are transported across the membrane together. An example is the symport in the intestinal mucosa that is responsible for the cotransport by facilitated diffusion of Na^+ and glucose from the intestinal lumen into mucosal cells.

viii. *Antiports* : They exchange one substance for another. The Na^+-K^+ ATPase is a typical antiport; it moves three Na^+ out of the cell in exchange for each two K^+ that it moves into the cell.

(Ref. Ganong 22th edition, Page 30, 31, 32)

Cytoplasm & its organelles

Cytoplsm

The cytoplasm is filled with both minute and large dispersed particles and organelles, ranging in size from a few nanometers to many micrometers. Clear fluid portion of cytoplasm in which the particles are dispersed is called *cytosol*; this contains mainly dissolved proteins, electrolytes and glucose.

Dispersed in the cytoplasm are nutral fat globules, glycogen granules, ribosomes, secretory vesicles & five specially important organelles- the *endoplasmic reticulum, the Golgi apparatus, mitochondria, lysosomes and peroxisomes.*

(Ref. Guyton & Hall- 11th Edition; page 14, 15)

Functions of cytoplasm

1. *Metabolic function:* Resulting in the synthesis of essential compounds for body growth and liberation of energy.
2. *Special functions :*
   i. *Irritability* : Ability to respond stimuli.
   ii. *Conductivity* : conducting an electrical disturbance in the form of impulse.
   iii. *Contractility* : Shortening or increasing the tension in response to stimulus.

Cell Organelles

The cell is not merely a bag of fluid, enzyms, and chemicals; it

also contains highly organized physical structures, many of which are called cell organelles.

The physical nature of each of these is equally as important to the function of the cell as the cell's chemical constituents. For instance, without one of the organelles, the mitochon-dria, more than 95 percent of the energy supply of the cell would cease immediately.

Five important cell organelles are :

1. Endoplasmic reticulum
2. Golgi apparatus
3. Mitochondria
4. Lysosomes
5. Peroxisomes.

(Ref. Guyton & Hall- 11th edition;Page-14 & 15 & others)

Endoplasmic Reticulum

These are the network of tubular and flat vesicular structures present in the cytoplasm. The tubules and vesicles inter-connect with one another.

Structure : The walls of the *endoplasmic reticulumn* are constructed of lipid bilayer membranes that contains large amounts of proteins, similar to the cell membrane. The total surface area of this structure in some cells- the liver cells, for instance- can be as much as 30 to 40 times as great as the cell membrane area.

The space inside the tubules and vesicles is filled with *endoplasmic matrix*, a watery fluid medium that is different from the fluid in the cytosal outside the endoplasmic reticulumn.

Types :

i. *Granular endoplasmic reticulum :* Outersurface is covered with ribosomes.
   Function : Synthesis of protein in the cell.

ii. *Agranular endoplasmic reticulum :* Outer surface is devoid of ribosome.
   Function : Synthesis of lipid substances and in many other enzymatic processes of the cell.

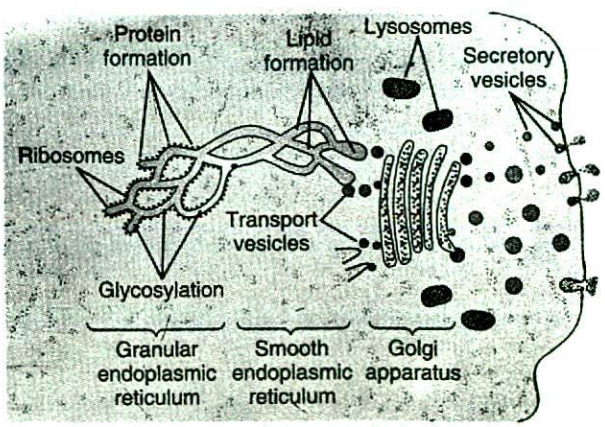


Fig: 1-3. Formation of proteins, lipids, and cellular vesicles by the endoplasmic reticulum and Golgi apparatus.

Functions of endoplasmic reticulum :

i. Synthesis of protein in the cell- by granular endoplasmic reticulum.

ii. *Agranular endoplasmic reticulum :* Synthesis of lipid substances and in many other enzymatic processes of the cell.

Other significant function of the endoplasmic reticulumn, especially the smooth reticulumn, incluide the following :

iii. It provides the enzymes that control glycogen breakdown when glycogen is to be used for energy.

iv. It provides a vast number of enzymes that are capable of detoxifying substances such as drugs that might damage the cell. It achives detoxification by coagulation, oxidation, hydrolysis, conjugation with glucuronic acid, or in other ways.

(Ref. Guyton & Hall- 11th page-15 & 20)

Ribosome

Ribosomes are minute granular particles measure approximately 22 by 32 nm.

Structure : The ribosomes are complex structures, containing many different proteins and at least three ribosomal RNAs.

Type :

1. Free ribosomes
2. Ribosomes attached with endoplasmic reticulum.

Function :

a. *Free ribosomes* :
   i. Synthesize cytoplasm proteins such as hemoglobin.
   ii. Synthesize proteins found in peroxisomes and mitochondria.

b. *Ribosomes attached with endoplasmic reticulumn* :
   i. Synthesize all transmembrane proteins.
   ii. Synthesize most secreted proteins.
   iii. Synthesize most proteins that are stored in the Golgi apparatus, lysosomes, and endosomes.

(Ref. Guyton & Hall- 11th Edi, P-15; Ganong 22th Edi, P-18)

Golgi Apparatus

It usually is composed of four or more stacked layers of thin, flat enclosed vesicles lying near one side of the nucleus .It is closely related to the endoplasmic reticulumn. The walls are constructed of lipid bilayer membranes that contains large amounts of proteins.

This apparatus is prominent in secretory cells; where it is located on the side of the cell from which the secretory substances are extruded.

(Ref. Guyton & Hall- 11th Edition; Page-15)

Function :

The Galgi apparatus functions in association with the endoplasmic reticulum.

i. Substances transported from the endoplasmic reticulum to the Galgi apparatus are then processed in the Golgi

apparatus to form lysosomes, secretory vesicles, or other cytoplasmic components.

ii. It is associated with transmission of secretory products.

iii. Intracellular vesicles formed by the Galgi apparatus replenishes the membranes.

iv. It has the capability of synthesizing certain carbhydrates that can not be formed in the endoplasmic reticulum i.e *hyaluronic acid* and *chondroitin sulfate.*

(Ref. Guyton & Hall- 11th Edition; Page-15 & 21)

Functions of the hyaluronic acid and *chondroitin sulfate :*

a. They are the major components of proteoglycans secreted in mucus and other glandular serretions.

b. They are the major components of the *ground substance* in the interstitial spaces, acting as filter between collagen fibers and cells.

c. They are principle components of the organic matrix in both cartilage and bone.

Types of vesicles formed by the Golgi apparatus :

i. Secretory vesicles

ii. Lysosomes.

Mechanism of transmission of secretory products : As substances are formed in the endoplasmic reticulum, especially the proteins, they are transported through the tubules towards the portions of smooth endoplamic reticulum that lie nearst the Golgi apparatus. At this point, small *transport vesicles* composed of small envelopes of smooth endoplasmic reticulum continually breaks away and diffuse to the *deepest layer* of Golgi apparatus. Inside the vesicles are the synthesized proteins and other products from the endoplasmic reticulum.

The transport vesicles instantly fuse with the Galgi apparatus and empty their contained substances into the vesicular spaces of Golgi apparatus. Here, additional carbohydrate moiety are added to the secretions. Also, a most important function of the Galgi apparatus is to compact the endoplasmic reticulum secretions into highly concentrated packets. As the secretion pass towards the outermost layers of the Golgi apparatus, the compaction and processing proceed. Finally both small and large vesicles continually break away from the Golgi apparatus, carrying with them the compacted secretory substances, and the vesicles diffuse throughout the cell.

(Ref. Guyton & Hall- 11th Edition; Page-21,22)

Lysosome

Lysosomes are vesicular organelles that form by breaking off from the Golgi apparatus and then dispersing throughout the cytoplasom.

a. *Diameter* : The lysosome is quite different in different types of cells, but it usually is 250 to 750 nanometers in diameter.

b. *Structure* : It is surrounded by a typical lipid bilayer membrane and is filled with large numbers of small granules 5 to 8 nanometers in diameter, which are protein aggregates of as many as 40 different hydrolase (digestive) enzymes. Ahydrolytic enzyme is capable of splitting an organic compound.

Ordinarily, the membrane surrounding the lysosome prevents the enclosed hydrolytic enzymes from coming in contact with other substances in the cell and, therefore, prevents their digestive actions.

Some of the enzymes found in lysosomes and the cell components that are their substrate :

Enzyme	*Substrate*
Ribonuclease	RNA
Deoxiribonuclease	DNA
Phosphatase	Phosphate esters
Glycosidases	Complex carbohydrates; glycosides polysaccharides
Arylsulfatases	Sulfate esters
Collagenase	Proteins
Cathepsins	Proteins

In certain genetic disorders of the body, some of the usual digestive enzymes are missing from the lysosomes, especially enzymes that are required to digest lipid aggregates or glycogen granules. In such instances, extreme quantities of lipids or glycogen often accumulate in the cells of many organs, especially in the liver, and lead to early death of the person.

Function of lysosome :

1. Lysosomes provide an *intracellular digestive system* that allows the cell to digest within itself-
   a. Damaged cellular structures.
   b. Food particles that have been ingested by the cell.
   c. Unwanted matter such as bacteria.
2. *Regression of tissues* : Tissues of the body often regress to smaller size. For instance, this occurs in the uterus after pregnancy, in muscles during long periods of inactivity, and in mammary glands at the end of lactation. Lysosomes are responsible for much of this regrssion. The mechenism by which lack of activity in a tissue causes the lysosomes to increase their activity is unknown.
3. *Removal of damaged cells or damaged portions of cells from tissues-* ***Autolysis of cells*** : Removal of damaged cells or damaged portions of cells from tissues- cells damaged by heat, cold, trauma, chemicals, or any other factor is another special role of the lysosomes.

   Damage to the cell causes lysosomes to rupture. The hydrolases begin immediately to digest the surrounding organic substances.

   i. *If the damage is slight*, only a portion of the cell is removed, followed by repair of the cell.

   ii. *If the damage is severe*, the enter cell is digested, a process called ***autolysis***. In this way, the cell is completely removed, and a new cell of the same type ordinarily is formed by mitotic reproduction of an adjacent cell to take the place of the old one.

4. The lysosomes also contain bactericidal agents that can kill phagocytized bacteria before they can cause cellular damage. These agents include *lysozyme* that dissolves the bacterial cell membrane, *lysoferrin* that binds iron and other metals that are essential for bacterial growth, and acid at a pH of about 5.0 that activates the hydrolases and inactivates some of the bacterial metabolic systems.

(Ref. Guyton 11th ed; P-16, 20; Ganong 22th ed, Page-11, 12)

Peroxisomess

Peroxisomes are similar physically to lysosomes. They are believed to be formed by self-replication (perhaps by budding off from the smooth endoplasmic reticulum). They contain oxidases.

Function : Several of the oxidases are capable of combining oxygen with hydrogen ions from different intracellular chemicals to form hydrogen peroxide (H_2O_2) . The hydrogen peroxide in turn is itself a highly oxidizing substance, and this is used in association with *catalase*, another oxidase enzyme present in large quantities in peroxisomes, to oxidize many substances that might otherwise be poisonous to the cell. For instance, about half the alcohol a person drinks is detoxified by the peroxisomes of the liver cells in this manner.

(Ref. Guyton Hall- 11th Edition; Page-16)

Difference between lysosomes and peroxisomes

Lysosomes	*Peroxisomes*
1 They are formed by breaking off from the Galgi apparatus.	1.They are formed by budding off from the smooth endoplasmic reticulum.
2. They contain hydrolases.	2.They contain oxidases.

(Ref. Guyton & Hall- 11th Edition; Page-16)

Secretory Vesicles

One of the important functions of many cells is secretion of special substances. Almost all such secretory substances are formed by the endoplasmic reticulum-Golgi apparatus system and are then released from the Golgi apparatus into the cytoplasm in the form of storage vesicles called secretory vesicles or ***secretory granules***.

Example : In pancreatic acinar cells, secretory vesicles store protein pro-enzymes (enzymes that are not activated). The pro-enzymes are secreted latter through the outer cell membrane into the pancreatic duct and thence into the duodenum, where they become activated and perform digestive functions on the food in the intestinal tract.

(Ref. Guyton & Hall- 11th Edition; Page-16)

Mitochondria

The mitochondria are the powerhouse of the cell. Total number per cell varies from less than one hundred upto several thousand. It is variable in size and shape, some are only a few hundred nanometers in diameter and globular in shape, where as others are as large as 1 micrometer in diameter, as long as 7 micrometers and branching or filamentous in shape.

The basic structure of the mitochondrion is composed mainly of two *lipid bilayer - protein membranes* : an outer membrane and an inner membrane. Many infolding of the inner membrane form shelves called cristae on to which oxidative enzymes are attached. In addition, the inner cavity of the mitochondrion is filled with a matrix containing large quantities of dissolved enzymes.

Mitochondria are self replicative, that means one mitochondrion can form a second one, a third one and so on, whenever there is need in the cell for increased amounts of ATP.

Function :

i. The enzymes of the mitochondria cause oxidation of the nutrients (carbohydrate, protein, and fat), thereby forming carbon dioxide & water and liberate energy. The liberated energy is used to synthesize a high energy substance called adenosine triphosphate (ATP).

   ATP is then transported out of the mitochondrion and it diffuses throughout the cell to release its energy wherever it is needed for performing cellular function.

ii. Mitochondria contain deoxyribonucleic acid (DNA) that controls replication of the cell.

(Ref. Guyton & Hall- 11th Edition; Page-16,17)

N.B. Sperms contribute few, if any, mitochondria to the zygote; so the mitochondria come almost entirely from the ovum and their inheritance is almost exclusively maternal.

(Ref. Ganong 22th Edition; Page-11)

Nucleus

The nucleus is the control center of the cell. It is concerned with the control of constructive and functional activities of the cell. The shape, size and number of nucleus vary with different types of cells.

During interphase a nucleus consists of -

i. *Nuclear membrane :* Under electron microscope, the nuclear membrane, a nuclear envelope is seen to consist of two layers and separates it from the surrounding cytoplasm. Each membrane layer is 70-80 Å thick. The nuclear evnelope is penetrated by several thousand nuclear pores. The pore is about 9 nanometers in diameter.

ii. *Nucleoplasm :* Also called nuclear sap or karyolymph. It is a viscid material more viscid than the cytoplasm which fills the space bound by the nuclear membrane.

iii. *Nucleoli (plasmosomes) :* The nuclei of most cells contain one or more lightly staining structures called nucleoli. It is not bound by membrane.

iv. *Chromatin granules :* These are the small granular element found within the nucleoplasm, which show intense staining reaction with basic coal tar dyes.

(Ref. Guyton & Hall- 11th Edition; Page-17, 18 & others)

Function of nucleus :

i. It is the dynamic centre of life as it controls nutritive and respiratory activites of the cells.
ii. It influences growth and initiates divisions or reproduction of cell.
iii. The DNA molecules of Nucleus act as regulator of synthesis of enzyme protein or proteins in the cytoplasm.
iv. The DNA also inherit the character to the offspring through genes.

N.B. Nucleus contains chromatin (DNA molecules); chromatin becomes chromosome during cell division; chromatin contains genes.

No centriole no mitosis. Vincristin (anticancer drug) acts by poisoning spindles and stoping mitosis; no mitosis possible in neurons.

DNA synthesizes RNA and RNA molecules stay in the cytoplasm, hanging from the endoplasmic reticulam as ribosomes or free in cytosol (free ribosomes).

There may be nucleolie in the nucleus where there is plenty of RNA molecules, otherwise RNA molecules found mainly in the cytoplasm.

Cytoskeleton

Definition : Cytoskeleton is a system of fibers that not only maintains the structure of the cell but also permits it to change shape and move.

All cell have cytoskeleton. The cytoskeleton is made up primarily of microtubules, intermediate filaments, and microfilaments, along with proteins that anchor them, tie them together, and in the case of microtubules and microfilaments move along them.

a. ***Microtubules*** : Microtubules are long, hollow structures with 5 nm walls surrounding a cavity 15 nm in diameter. They are made up of two globular protein subunits, alpha and beta tubulin. A third subunit, delta tubulin, is associated with the production of microtubules by the centrosomes.

Microtubules are a dynamic portion of the cell skeleton, because of their constant assembly and diassembly.

Function of microtubules :

i. They provide the tracks for transport of vesicles, organelles such as secretory granules, and mitochondria from one part of the cell to another.

Microtubules can transport in both directions, and indeed, the same microtubule has been transporting two particles in opposite directions.

ii. They form the spindle, which moves the chromosomes in mitosis.

Applied : Microtubules assemly is prevented by colchicine and vinblastine. The anticancer drug paclitaxel (*Taxol*) binds to microtubules and makes them so stable that organelles cannot move and mitotic spindles cannot form, leading to cell death.

b. ***Intermediate filaments*** : Intermediate filaments are 8-14 nm in diameter and are made up of various sub-units.

Some of these filaments connect the nuclear membrane to the cell membrane. They appear to be part of the cytoskeleton, but their exact function is not known.

c. ***Microfilaments*** : Microfilaments are long solid fibers 4-6 nm in diameter. They are made up of actin. Actin and its mRNA are present in all types of cells. It is the most abudant protein in mammalian cells, sometimes accounting for as much as 15% of the total protein in the cell. Actin by its interaction with myosin brings about contraction of muscle.

(Ref. Guyton & Hall-11th Edition & others)

Centrosomes

Near the nucleus in the cytoplasm of eukaryotic animal cells is a centrosome. The centrosome is made up of two centrioles and surrounding amorphous pericentriolar material.The centrioles are short cylinders located near the nucleus, and they are arranged so that they are at right angles to each other. Microtubules in groups of three run longitudinally in the walls of each centriole. There are nine of these triplets spaced at regular intervals around the circumference.

The centrosomes are microtubule-organizing centers (MTOCs) that contain gama tubulin. The microtubules grow out of this gama tubulin in the pericentriolar material. When a cell divides, the cetrosomes duplicate themselves, and the pairs move apart to form the poles of the mitotic spindle, which is made up of microtubules. In multinucleate cells, there is a centrosome near each nucleus.

Cell adhesion molecules

Cells are attached to the basal lamina and to each other by *cell adhesion molecules (CAMs)* that are prominent parts of the intercellular connections.

These adhesion proteins have attracted great attention in recent years because they are important in embryonic development and formation the nervous system and other tissues, in holding tissues together in adults, in inflammation and wound healing, and in the metastasis of tumours.

Many pass through the cell membrane and are anchored to the cyto- skeleton inside the cell. Some bind to like molecules on the other cells (homophilic binding) , where as others bind to other molecules (hetero philic binding). Many binds to laminas, a family of large cross-shape molecules with multiple receptor domains in the extracellular matrix.

Types of cell adhesion molecules :

1. *Integrins,* heterodimers that bind to various receptors.
2. Adhesion molecules of the *IgG superfamily of immunoglobulins*, some of which bind to other molecules and some of which bind homophilically.
3. *Cadherins*, Ca^{++} dependent molecules that mediate cell-to-cell adhesion by homophilic reactions.
4. *Selectins*, which have lectin like domains that bind carbohydrates.

The cell adhesion molecule not only fasten cells to their neighbour- they also transmit signals into and out of the cell.

(Ref. Ganong 22th edition; Page-15,16)

Intercellular Connections

Two types of Junctions:

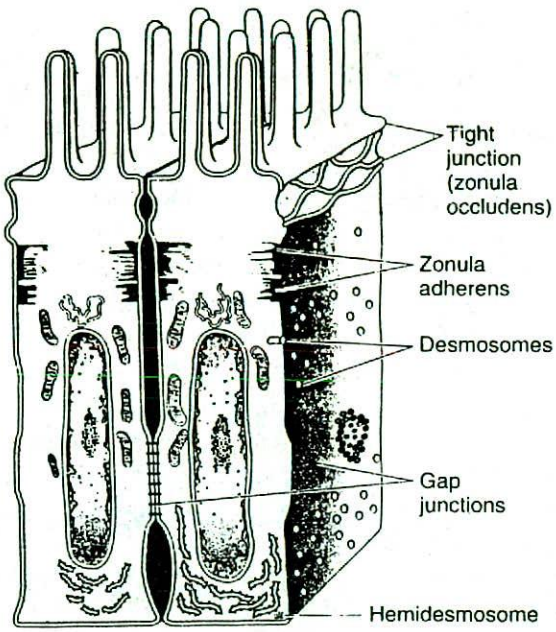
i. *Tight junction* or *Zonula occludens*: Junction that fasten the cells to one another and surrounding tissues.

ii. *Desmosome and zonula adherens* : Holds cells together.

iii. *Hemidesmosome and focal* : Attach cells to their basal lamina.

iv. *Gap junction* : Junctions that permit transfer of ions and other molecules from one cell to another.

Tight junction : It sorrounds the apical margins of the cells in epithelia such as the intestinal mucosa, the walls of the renal tubules, and the choroid plexus. They are made up of ridges half from one cell and half from the other which adhere so strongly at cell junctions that they almost obliterate the space between the cells. The ridges are made up of proteins.



Gap Junction : At gap junctions, the intercellular space narrows from 25 nm to 3 nm. Each cells are lined up with one another. When lined up with the channel in the corresponding connexon in the adjacent cell, permits substances to pass between the cells without entering the ECF. The diameter of the channel is normally about 2 nm, which permits the passage of ions, sugars, amino acids, and other solutes with the molecular weight upto 1000. Gap junctions thus permit the rapid propagation of electrical activity from cell to cell and the exchange of various chemical messengers.

(Ref. Ganong 22th Edition; Page-17)

Q. 01. **What do you mean by intercellular communications?**

Ans. *Intercellular communication* : Cells communicate with each other via chemical messengers. Within a given tissue, some messengers move from cell to cell via *gap junctions* without entering the ECF.

The chemical messengers include amines, amino acids, steroids, polypeptides, and in some instances lipids, purine nucleotides, and pyrimidine nucleotides. It is worth noting that in various parts of the body, the same chemical messenger can function as a neurotransmitter, a paracrine mediator, a hormone secreted by neurons into the blood (neural hormone), and a hormone secreted by gland cells into the blood.

Types : There are three general types of intercellular communication mediated by messengers in the ECF :

i. *Neural communication* : In which neurotrans-mitters are released at synaptic junctions from nerve cells and act across a narrow synaptic cleft on a postsynaptic cell.

ii. *Endocrine communication* : In which hormones and growth factors reach cells via the circulating blood.

iii. *Paracrine communication* : In which the products of cells diffuse in the ECF to affect neighboring cells that may be some distance away.

Autocrine communication : In addition, cells secrete chemical messengers that in some situations bind to receptors on the same cell, ie, the cell that secreted the messenger (autocrine communication).

Juxtacrine communication : An additional form of intercellular communication is called juxtacrine communication.

(Ganong 22th Edition, page-36,37)

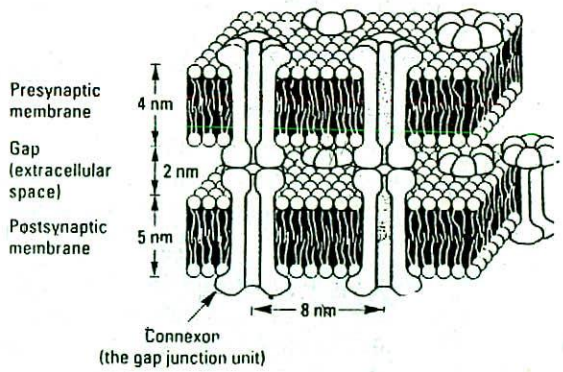


Fig : 1-4. *Intercellular Connections*

Functional systems of the cell

A. **Ingestion by the cell- Endocytosis** : If a cell is to live and grow and reproduce, it must obtain nutrients and other substances from the surrounding fluids. Most substances pass through the cell membrane by *diffusion* and *active transport.*

Diffusion means simple movement through the membrane caused by random motion of the molecules of the substances, moving either through cell membrane pores or, in the case of lipid soluble substances, through the lipid matrix of the membrane.

Active transport means actual carrying of a substance through the membrane by a physical protein structure that penetrates all the way through the membrane.

Very large particles enter the cell by a specialized function of the cell membrane called *endocytosis*. The principle forms of endocytosis are *pinocytosis* and *phagocytosis*.

(Ref. Guyton & Hall- 11th Edition; Page-19)

a. ***Pinocytosis*** : Pinocytosis means the ingestion of extremely small globules of extracellular fluid, forming minute vesicles in the cell cytoplasm.

Pinocytosis occurs continually at the cell membranes of most cells but specially rapidly in some cells. For instance, it occurs so rapidly in macrophages that about 3 per cent of the total macrophage membrane is engulfed in the form of vesicles each minute. Even so, the pinocytic vesicles are so small- usually only 100 to 200 nanometer in diameter- that most of them can be seen with the electron microscope.

Pinocytosis is the only means by which most large macromolecules, such as most protein molecule, can enter cells. In fact the rate at which pinocytic vesicles form usually is enhanced when such macromolecules attach to the cell membrane.

Mechenism :

1. Small globules of extracellular fluid such as protein molecules attaching to the cell membrane.
2. These molecules usually attach to specialized protein *receptors* on the surface of the membrane that are specific for the type of protein that is to be absorbed .
3. The receptors generally are concentrated in small pits on the outer surface of the cell membrane, called *coated pits*.
4. On the inside of the cell membrane beneath this pits is a laticework of fibrillar protein called *clathrin* as well as other proteins, perhaps including contractile filaments of actin and myosin.
5. Once the protein molecules have bound with the receptors, the surface properties of the cell membrane change in such a way that the enter pit invaginates inward and fibrillar proteins surrounding pit cause its borders to close over the attached proteins as well as over a small amount of extracellular fluid.
6. Immediately thereafter, the invaginaed portion of the membrane breaks away from the surface of the cell, forming a *pinocytic vesicles* inside the cytoplasm of the cell.

Requirements :

1. This process requires energy from within the cell; this is supplied by ATP.
2. It also requries the presence of calcium ions in the extracellular fluid, wich probably react with contractile protein filaments beneath the coated pits to provide the force for pinching the vesicles away from the cell membrane.

(Ref. Guyton & Hall- 11th Edition; Page-19)

b. ***Phagocytosis*** : Phagocytosis means ingestion of large particles, such as bacteria, cells, and portions of degerating tissue.

Only certain cells have the capability of phagocytosis, most notably the tissue macrophages and some of the white blood cells.

Mechenism : Phagocytosis is initiated when a particle such as a bacterium, a dead cell, or tissue debries binds with receptors on the suface of the phagocyte. In the case of bacteria, each bacterium is usually is already attached to a specific antibody, and it is the antibody that attaches to the phagocyte receptors, dragging the bacterium along with it.

1. The cell membrane receptors attach to the surface ligands of the particle.
2. The edges of the membrane arround the points of attachment evaginate outward within a fraction of a second to surround the entire particle ; Then, progressively more and more membrane receptors attach to the particle ligands, all this occuring suddenly in a zipperlike manner to form a closed *phagocytic vesicle*.
3. Actin and other contractile fibrils in the cytoplasm surround the phagocytic vesicle and contract arround its outer edge, pushing the vesicle to the interior.
4. The contractile proteins then pinch the vesicle off, leaving it in the cell interior.
5. Immediately thereafter, the invaginaed portion of the membrane breaks away from the surface of the cell, forming a *phagocytic vesicles* inside the cytoplasm of the cell.

(Ref. Guyton & Hall- 11th Edition; Page-19, 20)

B. **Digestion of pinocytic and phagocytic foreign substances in the cell-*function of the lysosomes*** :

Almost immediately after a pinocytic or phagocytic vesicle appears inside a cell, one or more lysosomes become attached to the vesicle and empty their acid hydrolases to the inside of the vesicle.

Thus, a *digestive vesicle* is formed in which the hydrolases begin hydrolyzing the proteins, carbohydrates, lipids, and other substances in the vesicle. The products of digestion are small molecules of amino acids, glucose, phosphates, and so forth that can diffuse through the membrane of the vesicle into the cytoplasm. What is left of the digestive vesicle, called the *residual body,* represents the undigestible substances. In most instances, this is finally excreted through the cell membrane by a process called *exocytosis,* which is essentially the opposite the endocytosis. Thus the pinocytic and phagocytic vesicle-lysosomes may be called the *digestive organs* of the cells.

1. *Regression of tissues* : Tissues of the body often regress to smaller size. For instance, this occurs in the uterus after pregnancy, in muscles during long periods of inactivity, and in mammary glands at the end of lactation. Lysosomes are responsible for much of this regrssion. The mechenism by which lack of activity in a tissue causes the lysosomes to increase their activity is unknown.

2. *Removal of damaged cells or damaged portions of cells from tissues- Autolysis of cells* : Removal of damaged cells or damaged portions of cells from tissues- cells damaged by heat, cold, trauma, chemicals, or any other factor is another special role of the lysosomes.
   Damage to the cell causes lysosomes to rupture. The hydrolases begin immediately to digest the surrounding organic substances.
   i. *If the damage is slight*, only a portion of the cell is removed, followed by repair of the cell.
   ii. *If the damage is severe*, the enter cell is digested, a process called *autolysis*. In this way, the cell is completely removed, and a new cell of the same type ordinarily is formed by mitotic reproduction of an adjacent cell to take the place of the old one.
3. The lysosomes also contain bactericidal agents that can kill phagocytized bacteria before they can cause cellular damage. These agents include *lysozyme* that dissolves the bacterial cell membrane, *lysoferrin* that binds iron and other metals that are essential for bacterial growth, and acid at a pH of about 5.0 that activates the hydrolases and inactivates some of the bacterial metabolic systems.

(Ref. Guyton 11th ed; P-16, 20; Ganong 22th ed; P-11,12)

C. **Synthesis and formation of cellular structures by the endoplasmic reticulum and the Golgi apparutus** :

1. ***Specific functions of the endoplasmic reticulum*** :
   Most of the synthesis begins in the endoplasmic reticulum. The products that are formed then passed on to the Golgi apparatus, where they are further processed before release into the cytoplasm.
   i. *Proteins are formed by the granular endoplasmic reticulum* : Protein molecules are synthesized within the structures of the ribosomes. The ribosomes extrude some of the synthesized protein molecules directly into the cytosal, but they are also extrude many more through the wall of the endoplasmic reticulum to the interior of the endoplasmic vesicles, tubules, that is, into the *endoplasmic matrix*.
   ii. *Synthesis of lipids by the endoplasmic reticulum, especially by the smooth endoplasmic reticulum* : The endoplasmic reticulum also synthesizes lipids, espicially phospholipids and cholesterol. These are rapidly incorporated into the lipid bilayer of the endoplasmic reticulum itself, thus causing the endoplasmic reticulum to grow more extensive. This occurs mainly in the smooth portion of the endoplasmic reticulum.
   To keep the endoplasmic reticulum from growing beyond the needs of the cell, small vesicles called *endoplasmic reticulum vesicles* (ER vesicles) or *transport vesicles* continually break away from the smooth reticulum; most of these vesicles then migrate rapidly to the Golgi apparatus.

   Other significant function of the endoplasmic reticulumn, especially the smooth reticulumn, incluide the following :
   iii. It provides the enzymes that control glycogen breakdown when glycogen is to be used for energy.
   iv. It provides a vast number of enzymes that are capable of detoxifying substances such as drugs that might damage the cell. It achives detoxification by coagulation, oxidation, hydrolysis, conjugation with glycuronic acid, or in other ways.

   (Ref. Guyton & Hall- 11thEdition; Page-20, 21)

2. ***Specific functions of the Golgi apparatus*** :
   i. *Synthetic function of the Golgi apparatus* : It has the capability of synthesizing certain carbohydrates that can not be formed in the endoplasmic reticulum i.e *hyaluronic acid* and *chondroitin sulfate*.
   Functions of the hyaluronic acid and chondroitin sulfate are as follows :
   a. They are the major components of proteoglycans secreted in mucus and other glandular secretions.
   b. They are the major components of the *ground substance* in the interstitial spaces, acting as filter between collagen fibers and cells.
   c. They are principle components of the organic matrix in both cartilage and bone.
   ii. *Processing of endoplasmic secretions by the Galgi appatus- Formation of Vesicles* : As substances are formed in the endoplasmic reticulum, especially the proteins, they are transported through the tubules towards the portions of smooth endoplamic reticulum that lie nearst the Golgi apparatus. At this point, small *transport vesicles* composed of small envelopes of smooth endoplasmic reticulum continually breaks away and diffuse to the *deepest layer* of Golgi apparatus. Inside the vesicles are the synthesized proteins and other products from the endoplasmic reticulum.
   The transport vesicles instantly fuse with the Galgi apparatus and empty their contained substances into the vesicular spaces of Golgi apparatus. Here, additional carbohydrate moiety are added to the secretions. Also, a most important function of the Galgi apparatus is to compact the endoplasmic reticulum secretions into highly concentrated packets. As the secretion pass towards the outermost layers of the Golgi apparatus, the compaction and processing proceed. Finally both small and large vesicles continually break away from the Golgi apparatus, carrying with them the compacted secretory substances, and the vesicles diffuse throughout the cell.

To give an idea of the timing of these processes : When a glandular cell is bathed in radioactive amino acids, newly formed radioactive protein molecules can be detected in the granular endoplasmic reticulum within 3 to 5 minutes. Within 20 minutes, newly formed proteins are already present in the Golgi apparatus, and within 1 to 2 hours, radioactive proteins are secreted from the surface of the cell.

(Ref. Guyton & Hall- 11th Edition; Page-21)

Types of vesicles formed by the Golgi Apparatus- *Secretory Vesicles and Lysosome* : In a highly secretory cell, the vesicles formed by the Golgi apparatus are mainly *secretory vesicles* containing protein substances that are to be secreted through the surface of the cell membrane. These secretory vesieles first diffuse to the cell membrane, then fuse with it and empty their substances to the exterior by the mechanism called *exocytosis*. Exocytosis, in most cases, is stimulated by the entry of calcium ions into the cell; calcium ions interact with the vesicular membrane in some way that is not understood and cause its fusion with the cell membrane, followed by exocytosis- that is, opening of the membrane's outer surface and extrusion of its contents outside the cell.

Some vesicles, however, are destined for intracellular use.

(Ref. Guyton & Hall- 10th Edition; Page-18,19)

Use of intracellular vesicles to replenish cellular membrane : Others of the intracellular vesicles formed by the Golgi apparatus fuse with the cell membrane or with the membranes of intracellular structures such as the mitochondria and even the endoplasmic reticulum. This increases the expanse of these membranes and there by replinishes the membranes as they are used up. For instance, the cell membrane loses much of its substance every time it forms a *phagocytic* and *pinocytic vesicle*, and it is vesicles from the Golgi apparatus that continually replenish the cell membrane.

In summary, *the membranous system of the endoplasmic reticulum and Golgi appatatus represents a highly metabolic organ capable of forming new intracellular structures as well as secretory substances to be extruded from the cell.*

(Ref. Guyton & Hall- 11th Edition; Page-21)

D. **Extraction of energy from nutrients-** ***Functions of the mitochondria*** : The principal substances from which cells extract energy are the foodstuffs that react with oxygen- carbohydrates, fats, and proteins. In the human body, essentially all carbohydrates are converted into glucose by the digestive tract and liver before they reach the cell. Similarly, the proteins are converted into amino acids and the fats into fatty acids. Inside the cell, foodstuffs react chemically with the oxygen under the influence of various enzymes that control the rates of the reactions and channel the energy that is released in the proper direction.

Briefly, almost all these oxidative reactions occur inside the mitochondria, and the energy that is released is used to form the high energy compound adenosine triphosphate (ATP). Then, the ATP, not the original foodstuffs themselves, is used throughout the cell to energize almost all the subsequent intracellular metabolic reactions.

(Ref. Guyton & Hall- 11th Edition; Page-22)

Transport Across Cell Membranes

Transport across cell membranes is accomplished primarily by *exocytosis, endocytosis, movement through ion channels, primary and secondary active transport.*

Exocytosis

Difinition : Extrusion of proteins from cell to the surrouding fluid is called exocytosis. It requires ca^{++} and energy, along with proteins.

Process : Proteins that are secreted by cells move from the endoplasmic reticulum to the Golgi apparatus, and from the trans golgi, they are extruded into secretory granules or vesicles. The graules and vesicles move to the cell membrane. Their membrane then fuses to the cell membrane and the area of fusion breaks down. This leaves the contents of the granules or vesicles outside the cell and the cell membrane becomes intact.

Pathways :

1. Nonconstitutive pathway : Proteins from the Golgi apparatus initially enters secretory granules, where processing of prohormones to mature hormones occurs before exocytosis.
2. Constitutive pathway : Involves the prompt transport of proteins to the cell membrane in vesicles, with little or no processing or storage.

Endocytosis

Ingestion of nutrients and other substances from the surrounding fluid by the cell is called endocytosis.

Two principal forms of endocytosis are- *pinocytosis & phagocytosis.*

Phagocytosis : It is the process by which bacteria, dead tissues, or other bits of material visible under the microscope are engulfed by cells such as the polymorpho nuclear leucocytes of the blood.

Process : The material makes contact with the cell membrane, which then invaginates. The invagination is pinched off, leaving the engulfed material in the membrane enclosed vacuole and the cell membrane intact.

Pinocytosis *(cell drinking)* : It means the ingestion of extremely small substances that are in solution and hence not visible under the microscope.

Each types of endocytosis can be-

1. *Constitutive* : It is a continues process that is not induced.
2. *Receptor mediated* : It is produced for the most part via specialized clathrin coated pits on the cell membrane. It is triggered by various ligands binding to their receptors on

the cell membrane. Receptor mediated endocytosis occur more rapidly than constitutive endocytosis.

Types of endocytosis :

Types of endocytosis	*Size of vesicle or vacuole*	*Intermediate organelle*
Phagocytosis		
Receptor mediated	0.1-10 mm	Phagosome
Non-receptor mediated	0.1-10 mm	Vacuole
Pinocytosis		
Clathrin dependent		
Receptor mediated	100 nm	Endosome
Synaptic vesicle retrieval	50 nm	Endosome
Clathrin-independent		
Potocytosis	60 nm	Caveolae
Micropinocytosis	100 nm	Micropinosome
Maeropinocytosis	0.5-6 mm	Macropinosome

Osmosis

Definition : Migration of solvent from the solution of lower concentration to the higher concentration, when they are seperated by a semipermeable membrane is called Osmosis.

Rate of osmosis depends upon :

i. Difference in osmotic pressure of the solution.
ii. Permeability of the membrane.
iii. Electrical potential across the membarane and charge upon the wall and pore of the membrane.

Osmotic pressure : The force (pressure) by which the osmosis occurs is called osmotic pressure.

Physiological importance :

i. Absorption from the intestine.
ii. Exchange in the capillary bed.
iii. Regulation of urine formation.
iv. Continuous osmotic exchange between plasma and red cells.
v. *Clinical use*- injection of saline are given by way of treatment.

Q. ***On which factors osmotic pressure depends and why?***

Ans. Osmotic pressure depends upon the total number of the particles per unit volume but not upon the size of the molecules.

Because each particle in a solution exerts, on the average, the same amount of pressure against the membrane.

Q. ***Do you think crystaloid particles exert more osmotic pressure than colloid particles, why?***

Ans. Yes, crystaloid particles exert more osmotic pressure. Because, ionisable particle exert more osmotic pressure than non-ionised particles.

Q. ***Why ionise particle exert more osmotic pressure than non-ionised particles?***

Ans. A substance, which ionises has more number of osmotic particle, so osmotic pressure of ionised substance is more than of non-ionised substance.

Relation between osmolality to osmotic pressure :

At nomal body temperature, 1 milliosmole per liter concentration is equivalent to 19.3 mm Hg of osmotic pressure.

So, Osmotic pressure (mm Hg) = 19.3 x Osmolality (milli osmole /L)

Diffusion

Definition : The continual movement of molecules in a solution from a higher concentration to lower concentration is called diffusion.

Diffusion depends upon the weight and size of the molecules.

Physiological importance of diffusion :

i. Admixture of food stuffs with digestive juice.
ii. Absorption from the intestine.
iii. Exchange between plasma and red cells.
iv. Exchange in the capillary bed.
v. Admixture of gases in the lungs.

Factors affect the rate of diffusion :

1. *Concentration gradient :* The greater the concentration difference, the greater is the rate of diffusion.
2. *Molecular diameter :* The less the diameter of the molecule, the greater is the rate of diffusion.
3. *Distance between the area :* The shorter is the distance, the greater is the rate of diffusion.
4. *Cross section :* The greater the cross section of the chamber in which the diffusion is taking place, the greater is the rate of diffusion.
5. *Temperature :* The greater the temperature, the greater is the rate of diffusion.

Diffusion rate =

$$\frac{\text{Concentration difference x cross sectional area x temperature}}{\sqrt{\text{Molecular weight x distance}}}$$

Types of diffusion

i. *Simple diffusion :* Some lipid soluble substances (O_2, CO_2, alcohol, and fatty acids. can easily diffuse through the cell membrane, called simple diffusion. Here carrier is not required.
ii. *Facilitated diffusion :* Some lipid insoluble subs tance (glucose etc) can diffuse through the lipid matrix of cell membrane with the help of carrier mechanism called facilated diffusion. Here carrier is required.

Factors essential for facilitated diffusion

i. Concentration gradient
ii. Amount of carrier
iii. Enzyme.
iv. The rapidity with which the chemical reaction involved in the mechanism takes place.

Difference between the simple and facilitated diffusion

Simple diffusion	*Facilitated diffusion*
i. Carrier is not needed.	i. Carrier must be present.
ii. Rate of diffusion is almost exactly proportional to the difference of the concentration of particle on the two side of the membrane.	ii. For a carrier transported substance, rate of diffusion approches a maximum, as the concentration of the substance increase.

Passive transport

The movement of substance across the cell membrane along the concentration gradient is called passive transport.

The gradients are -

i. Osmotic pressure
ii. Hydrostatic pressre
iii. Gradient of concentration and potential.

Tyses :

i. Diffusion.
ii. Osmosis.
iii Filtration.
iv. Flow due to gravity.

Filtration

a. *Definition* : It is the process by which undissolved particles are separated from a liquid through a membrane as a result of mechanical force (filtering force).
b. *Filtering force* :
   i. Gravity.
   ii. Hydrostatic pressure.
c. *Filtering membrane* :
   i. Cloth
   ii. Filter paper
   iii. Membrane.
d. *Filtration depends on* :
   i. Pressure difference across the filtering membrane.
   ii. Pore size of the membrane
   iii. Osmotic pressure of the fluid to be filtered
e. *Improtance* :
   i. Absorption from the small intestine.
   ii. Passage of water, salts, food stuff etc. from the blood stream to the tissue fluid.
   iii. Formation of urine
   iv. Formation of CSF.

Movement through ion channels

Most ion channels probably evolved by gene duplication and divergence from an ancestral molecule with six membrane spanning segments. The wide diversity in ion channel properties permits ion transport.

1. *Na^+ channels :* They are tetramers, with each subunit crossing the membrane six times.
2. *K^+ channels :* They are tetrameric. Their subunits are encoded by a number of different genes, and many of the genes are able to generate different domain structures by alternate splicing.
3. *Cl^- channels :* They are involved for the most part in volume regulation of cells, in transepithelial ion transport and apparently in regulation of muscle and kidney function. For example GABA receptor and the glycine receptor are Cl channels.
4. *Ca^{++} channel* etc.

Cardiac ion channels :

i. *Voltage-gated channels*
   Na^+
   T Ca^{2+}
   L Ca^{2+}
   K^+
   Inward rectifying
   Delayed rectifying
   Transient outward
ii. *Ligand-gated K^+ channels* :
   Ca^+ activated
   Na^+ activated
   ATP-sensitive
   Acetylcholine-activated
   Arachidonic acid-activated.

(Ref. Ganong 21th edition, Page 80)

Potassium (K^+) channel

Most K^+ channels are tetramers, with each of the four sub-units forming part of the pore through which K^+ ions pass. Their subunits are encoded by a number of different genes, and many of the genes are able to generate different domain structures by alternate splicing. Fast-inactivating voltage-gated K^+ channels have a unique feature. Each of the tetramers has a polypeptide ball structure on the end of a polypeptide chain, and the ball moves into the channel, producing inactivation *(Fig. 1-31 Ganong)*. There are ball-and-chain structures on all four tetramers even though there is only one K^+ pore. In the acetylecholine ion channel and other ligand-gated cation or anion channels, five subunits make up the pore.

(Ref. Ganong 22th edition, Page 32)

Function and mechenism : The repolarization (phase 3) to the resting membrane potential (phase 4) is due to closure of the Ca^{++} channels and K^+ efflux through various types of K^+ channels. There are *three types of K^+ channels that produce repolarization* :

i. The first produces a *transient, early outward current* (I_{TO}) that produces an early incomplete repolarization.
ii. The second is *inwardly rectifying*, ie, at plateau potentials it allows K^+ influx but resists K^+ efflux and only at lower membrane potentials does it permit K^+ efflux. The current it produces is called I_{kr}.

iii. The third type is a *slowly activating (delayed rectifying)* type that produces a current called I_{ks}.

The sum of I_{kr} and I_{ks} is a small net outward current that increases with time and produces repolarization.

The subunits that make up the K^+ channels responsible for I_{kr} cross the membrane six times and are the product of HERG (for *human ether-a-go-go-related gene*). The channel responsible for I_{ks} is made up of a protein that crosses the membrane six times combined with a small protein called **minK** (because of its size) that has only a single membrane-spanning domain.

(Ref. Ganong 21th edition, Page 80)

a. ***In the heart***, repolarization is due to net K^+ efflux through three types of K^+ channels. Rhythmically discharging cells have a membrane potential that, after each impulse, declines to the firing level. Thus, this prepotential or pacemaker potential triggers the next impulse. At the peak of each impulse, Ik begins and brings about repolarization. Ik then declines, and as K^+ efflux decreases, the membrane begins to depolarize, forming the first part of the prepotential.

Applied : When the cholinergic vagal fibers to nodal tissue are stimulated, the membrane becomes hyperpolarized and the slope of the prepotentials is decreased because the acetylcholine released at the nerve endings increases the K^+ conductance of nodal tissue. This action is mediated by M_2 muscarinic receptors, which, via the $\beta\gamma$ subunit of a G protein, open a special set of K^+ channels. The resulting I_{KAch} counters the decay of I_k.

(Ref. Ganong 22th edition, Page 548, 549)

b. ***In the nerve***, a *third factor producing repolarization* is the opening of *voltage-gated* K^+ channels. This opening is slower and more prolonged than the opening of the Na^+ channels, and consequently, much of the increase in K^+ conductance comes after the increase in Na^+ conductance. The slower opening and delayed closing of the voltage-gated K^+ channels also explain accommodation. If depolarization occurs rapidly, the opening of the Na^+ channels overwhelms the repolarizing forces, but if the induced depolarization is produced slowly, the opening of K^+ channels balances the gradual opening of Na^+ channels, and an action potential does not occur.

(Ref. Ganong 22th edition, Page 59)

c. ***Slow postsynaptic potentials*** : Slow EPSPs and IPSPs have been described in autonomic ganglia, cardiac and smooth muscle, and cortical neurons. These postsynaptic potentials have a latency of 100-500 ms and last several seconds. The slow EPSPs are generally due to decreases in K^+ conductance, and the slow IPSPs are due to increases in K^+ conductance. In sympathetic ganglia, there is also a late slow EPSP that has a latency of 1-5 seconds and lasts 10-30 minutes. This potential is also due, at least in part, to decreased K^+ conductance, and the transmitter responsible for the potential is a peptide very closely related to GnRH, the hormone secreted by neurons in the hypothalamus that stimulates LH secretion.

(Ref. Ganong 22th edition, Page 90)

d. ***In vascular smooth muscle*** : Vascular smooth muscle cells provide an interesting example of the way high and low cytosolic Ca^{++} can have different and even opposite effects. In these cells, influx of Ca^{++} via voltage-gated Ca^{++} channels produces a diffuse increase in cytosolic Ca^{++} that initiates contraction. However, the Ca^{++} influx also initiates Ca^{++} release from the sarcoplasmic reticulum via ryanodine receptors and the high local Ca^{++} concentration produced by these Ca^{++} sparks increases the activity of ***Ca^{++}-activated K^+ channels*** in the cell membrane. These are also known as big K or ***BK channels*** because K^+ flows through them at a high rate. The increased K^+ efflux increases the membrane potential, shutting off voltage-gated Ca^{++} channels and producing relaxation. The site of action of the Ca^{++} sparks is the β_1-subunit of the *BK channel*, and mice in which this subunit is knocked out develop ***increased vascular tone*** and ***blood pressure***. Obviously, therefore, the sensitivity of the β_1-subunit to Ca^{++} sparks plays an important role in the control of vascular tone.

(Ref. Ganong 22th edition, Page 580)

Active Transport

a. *Definition* : The movement of substance across the cell membrane against the concentration gradient with active expenditure of energy by the help of carrier called active transport.

The energey is derived from ATP and the carriers are present in the cell membrane.

Each type of carrier transports only a specific substance.

b. *The gradient may be :*
   i. Electrical.
   ii. Pressure.
   iii. Concentration
   iv. Speed of flow.

c. *Active transport generally requires :*

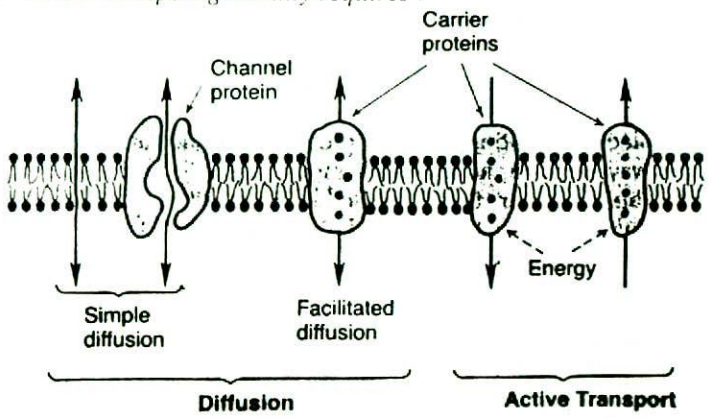


Fig. 1-5. *Transport pathways through the cell membrane and the basic mechanisms of transport.*

i. Active expenditure of energy
ii. Special carrier system
iii. Difference of concentration gradient
iv. Enzymes.

d. *Types of active transport* -
   i. Primary active transport.
   ii. Secondary active transport.
      1. Co-transport
      2. Counter transport.

   Active transport is divided into two types according to the source of the energy used to cause the transport. They are called primary active transport and secondary active transport.

(Ref. Guyton & Hall- 11th Edition; Page-52)

Primary active transport

In primary active transport, the energy is derived directly from the breakdown of adenosine triphosphate (ATP) or some other high energy phosphate compound. Transport depends on carrier proteins that penetrate through the membrane ie *Na^+-K^+ pump.*

(Ref. Guyton & Hall-11th Edition; Page-53)

Na^+-K^+ pump : Sodium-potassium pump refers to the mechanism that transports sodium ions out of the cells to the exterior and at the same time pumps potassium ions from the outside to the inside. Here two K^+ ions are transferred for each three Na^+ ions.

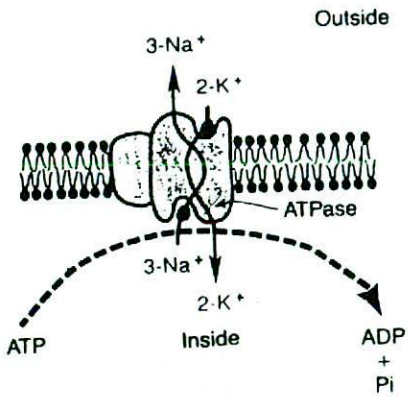


Fig : 1-6. *Sodium-potassium pump*

a. *Structure* : The carrier protein of the N^+-K^+ pump is a complex of two separate globular proteins, a larger one (molecular weight 100,000) and a smaller one (molecular weight 45,000). The function of the smaller protein is not known. *The larger protein has three specific features that are important for function of the pump* :
   i. It has three *receptor sites for binding sodium ions* on the portion of the protein that protrudes to the interior of the cell.
   ii. It has two *receptor sites for potassium ions* on the outside.
   iii. The inside portion of this protein adjacent to or near to the sodium binding sites has ATPase activity.

b. *Mechanism* : When 3 Na^+ ions bind on the inside of the carrier protein and 2 K^+ ions on the outside, the ATPase function becomes activated. This then leaves 1 molecule of ATP, splitting it to ADP and liberating a high energy phosphate bond of energy. This energy is then believed to cause a conformational change in the protein carrier molecule, extruding the sodium ions to the outside and potassium ions to the inside.

c. *Importance of Na^+-K^+ pump* : This pump is responsidble for-
   i. Maintaining the sodium and potassium concentration difference across the cell membrane
   ii. Establishing a negative electrical potential inside the cells.
   iii. The pump is so important to many different functioning systems of the body such as to nerve & muscle fibres for transmission of impulses, various glands for the secretion of different substances, and all the cells of the body to prevent cellular swelling.
   iv. ***Importance of the Na^+-K^+ pump in controlling cell volume*** : *The mechanism for controlling the volume is as follows* :
      1. Inside the cell are large numbers of proteins and other organic compounds that cannot escape from the cell. Most of these are negatively charged and therefore collect around them large numbers of positive ions as well. All these substances then tend to cause *osmosis of water* to the interior of the cell. Unless this is checked, the cell will swell indefinitely until it bursts. The normal mechanism for preventing this is the Na^+-K^+ pump.
      2. *Na^+-K^+ pump* pumps three Na^+ ions to the outside of the cell for every two K^+ ions pumped to the interior. Also, the membrane is far less permeable to sodium ions than to potassium ions, so that once the sodium ions are on the outside, they have a strong tendency to stay there. Thus, this represents a continual net loss of ions out of the cell, which initiates osmosis of water out of the cell as well.
      3. If a cell begins to swell for any reason, this automatically activates the Na^+-K^+ pump, moving still more ions to the exterior and carrying water with them.

   Therefore, the Na^+-K^+ pump performs a continual surveillance role in maintaining normal cell volume.

(Ref. Guyton & Hall- 11th Edition; Page-53, 54)

Electrogenic pump

i. *Definition* : Na^+-K^+ pump creates an electrical potential across the cell membrane because in every pump cell loses one positive charge; so Na^+-K^+ pump is called electrogenic pump.

ii. *Stimulatory factors* :
   a. Aldosterone, thyroid hormones increase the formation of

Na^+-K^+ATPase molecule, and thus increase Na^+-K^+ pump.

b. Insulin increases Na^+-K^+ pumps activity probably by a variety of different mechanisms.

iii. *Inhibitory factors* :

a. The activity of the Na^+-K^+ pump is inhibited by cardiac glycosides (digitalis) - due to inhibition of Na^+-K^+ ATPase.

b. Dopamine in the kidney inhibits the Na^+-K^+ pump by phosphorylating Na^+-K^+ ATPase.

(Ref. Guyton & Hall- 11th Edition; Page-53, 54)

Primary active transport of calcium : Calcium ions are normaly maintained at extremely low concentration in the intracellular cytosol of virtually all cells in the body, at concentration about 10,000 times less than that in the extracellular fluid. This is achieved mainly by two primary active transport calcium pumps. *One* is in the cell membrane and pumps calcium to the outside of the cell. The *other* pumps calcium ions into one or more of the internal vesicular organelles of the cell such as into the sarcoplasmic reticulum of muscle cell and into the mitochondria in all cells. In each of these instances, the carrier protein penetrates the membrane from side to side and also serves as an ATPase, having the same capability to cleave ATP as the ATPase sodium carrier protein. The difference is that this protein has a highly specific binding site for calcium instead of sodium.

(Ref. Guyton & Hall- 11th Edition; Page-54)

Primary active ransport of hydrogen ions : At two places in the body are important primary active transport systems for hydrogen ions. They are-

i. In the gastric glands of the stomach .

ii. In the late distal tubules and cortical collecting ducts of the kidneys.

In the gastric glands, the deep-lying *parietal cells* have the most potent primary active mechanism for transporting hydrogen ions of any part of the body. This is the basis for secreting hydrochloric acid in the stomach digestive secretions. At the secretory side of the parietal cells, the hydrogen ion concentration can be increased as much as a million fold and then released in association with chloride ions in the form of hydrochloric acid.

In the renal tubules there are special intercalated cells in the late distal tubules and cortical collecting ducts that also transport hydrogen ions by primary active transport. In this case, large amounts of hydrogen ions are secreted into the tubules to eliminate them from the body for the purpose of controlling the blood hydrogen ion concentration. The hydrogen ions can be secreted against a concentration gradient of about 900 fold.

At many other points in the body, hydrogen ions are transported by secondary active transport, but in these instances, they usually are transported against far less concentration gradients, such as 4 to 1 up to 10 to 1.

(Ref. Guyton & Hall- 11th Edition; Page-54)

N.B. Energetics of promary active transport : Pl. follow Guyton 11th Edition, Page 54.

Secondary active transport

In secondary active transport, the energy is derived secondarily from energy that has been stored in the form of ionic concentration differences between the two sides of a membrane, created in the first place by primary active transport.

Depends on : Transport depends on carrier proteins that penetrate through the membrane.

Types :

i. Co-transport

ii. Counter transport.

(Ref. Guyton & Hall- 11th Edition; Page-54)

i. **Co-transport** : When sodium ions are transported out of cells by primary active transport, a large concentration gradient of sodium usually develops very high concentration outside the cell and very low concentration inside. This gradient represents a storehouse of energy because the excess sodium outside the cell membrane is always attempting to diffuse to the interior. Under the appropriate conditions, this diffusion energy of sodium can literally pull other substances along with the sodium through the cell membrane. This phenomenon is called co-transport; it is one form of secondary active transport.

For sodium to pull another substance along with it, a coupling mechanism is required. This is achieved by means of still another carrier protein in the cell membrane. The carrier in this instance serves as an attachment point for both the sodium ion and the substance to be co-transported. Once they both are attached, a conformational change occurs in the carrier protein, and the energy gradient of the sodium ion causes both the sodium ion and the other substance to be transported together to the interior of the cell.

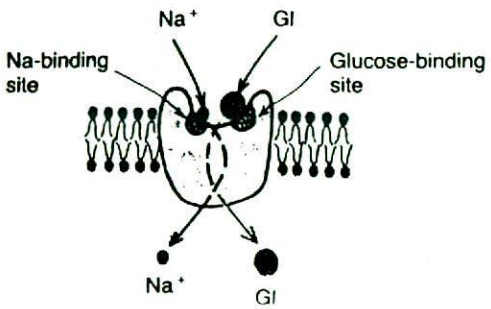


Fig. 1-7. *Postulated mechanism for sodium co-Transport of glucose.*

Co-transport of glucose and amino acids along with sodium ions : *Glucose and many amino acids* are transported into most cells against large concentration gradients; the mechanism of this is entirely by

the co-transport mechanism. The transport carrier protein has two binding sites on its exterior side, one for sodium and one for glucose. Also, the concentration of sodium ions is very high on the outside and very low inside, which provides the energy for the transport. A special property of the transport protein is that the conformational change to allow sodium movement to the interior will not occur until a glucose molecule also attaches. But when they are both attached, the conformational change takes place automatically, and both the sodium and the glucose are transported to the inside of the cell at the same time. Hence, this is a sodium-glucose co-transport mechanism.

Sodium co-transport of the amino acids occurs in the same manner as for glucose, except that it uses a different set of transport proteins. Five amino acid transport proteins have been identified, each of which is responsible for transporting one subset of amino acids with specific molecular characteristics.

Sodium co-transport of glucose and amino acids occurs especially in the epithelial cells of the intestinal tract and renal tubules to aid in the absorption of these substances into the blood.

(Ref. Guyton & Hall- 11th Edition; Page-54)

Other important co-transport mechanisms in at least some cells include co-transport of chloride ions, iodine ions, iron ions, and urate ions.

(Ref. Guyton & Hall- 11th Edition; Page-54)

ii. **Counter transport** : In counter-transport, sodium ions again attempt to diffuse to the interior of the cell because of their large concentration gradient. However, this time, the substance to be transported is on the inside of the cell and must be transported to the outside. Therefore, the sodium ion binds to the carrier protein where it projects through the exterior surface of the membrane, whereas the substance to be counter-transported binds to the interior projection of the carrier protein. Once both have bound, a conformational change occurs again, with the energy of the sodium ion moving to the interior causing the other substance to move to the exterior.

(Ref. Guyton & Hall-11th Edition; Page-54)

Sodium counter-transport of calcium and hydrogen ions : Two especially important counter-transport mechanisms are *sodium-calcium counter-transport* and *sodium-hydrogen counter-transport*.

a. *Sodium-calcium counter-transport* occurs through all or almost all cell membranes, with sodium ions moving the interior and calcium ions, to the exterior, both bound to the same transport protein in a counter-transport mode. This is in addition to primary active transport of calcium that occurs in some cells.

b. *Sodium-hydrogen counter-transport* occurs in several tissues. An especially important example is in the proximal tubules of the kidneys, where sodium ions move from the lumen of the tubule to the interior of the tubular cells, whereas hydrogen ions are counter transported into the lumen. This mechanism is not nearly so powerful for concentrating hydrogen ions as is the primary active transport of hydrogen that occurs in some of the more distal renal tubules, but it can transport such large numbers of hydrogen ions that it is nevertheless a key to hydrogen ion control in the body fluids.

(Ref. Guyton & Hall- 11th Edition; Page-55)

Membrane Potential

Membrane Potential

Definition : The electrical potential difference across the membrane is called *membrane potential.*

Membrance potentials (potential difference between the outside and inside of the cell memrane) are of 2 types-

a. Resting membrane potential (RMP)
b. Action potential.

Resting membrane potential

Definition : The electrical potential difference across the membrane at resting condition is called resting membrane potential.

The membrane potential of a nerve fiber is -90 mV. It is always expressd in negative because the inside of the cell membrane is always negatively charged in relation to the exterior as the cell membrane are impermeable to intracellular protein and other anions.

Causes : Two basic means by which membrane potentials can develop are :

i. Diffusion of ions through the membrane as a result of ion concentration differences between the two sides of the membrane i.e diffusion of potassium and sodium ions. The emphasis is on potassium leakage because, on average, the *potassium-sodium 'leak' channels* are far more permeable to potassium than to sodium, normally about 100 times as permeable. Which gives an internal potential of -86 millivolts.

ii. Active transport of ions through the membrane i.e sodium-potassium pump. Which gives an internal potential of -4 millivolts.

So the net membrane potential of a nerve membrane is -90 millivolts.

(Ref. Guyton & Hall-11th Edition; Page 59, 60)

Origin of normal resting membrane potential *(In a nerve membrane)* :

1. *Contribution of the potassium diffusion potential* : Because of high ratio of potassium ions inside to outside of the cell

membrane, 35 to 1, the Nernst potential corresponding to this ratio is -94 millivolts. Therefore, if potassium ions were the only factor causing the resting potential, this resting potential inside the fiber also would be equal to -94 millivolts.

2. *Contribution of sodium diffusion through the membrane* : Slight permeability of the nerve membrane to sodium ions, caused by the minute diffusion of sodium ions through the K^+-Na^+ *leak channels*. The ratio of sodium ions from inside to outside the membrane is 0.1, and this gives a calculated Nernst potential for the inside of the membrane of +61 millivolts.

   What will be the summated calculation of no. 1 and no. 2 : The membrane is highly permeable to potassium but only slightly permeable to sodium, it is logical that the diffusion of potassium contributes far more to the membrane potential than does the diffusion of sodium. In the normal nerve fiber, the permeability of the membrane to potassium is about 100 times as great as to sodium. Using this value in the Goldman equation gives an internal membrane potential of -86 millivolts, which is near to the potassium potential.

3. *Contribution of the Na^+-K^+ pump* : This provide still an additional contribution to the resting potential. Continuous pumping of three sodium ions to the outside for each two potassium ions pumped to the inside of the membrane.The fact that more sodium ions are being pumped to the outside than potassium to the inside causes a continual loss of positive charges from inside the membrane; this creates an additional degree of negativity (about -4 milivolts additional) on the inside beyond that which can be accounted for by diffusion alone. The net membrane potential with all these factors operative at the same time is about -90 milivolts.

In summary, the diffusion potentials alone caused by potassium and sodium diffusion would give a membrane potential of about -86 milivolts, almost all of this being determined by potassium diffusion. Then, an additional -4 milivolts is contributed to the membrane potential by the continuously acting electrogenic Na^+-K^+ pump, giving a net membrane potential of -90 milivolts.

(Ref. Guyton & Hall-11th Edition; Page-60, 61)

Resting membrane potential in different cell

Resting membrane potential in different cell are as follows :

1. Nerve fibers	:	-90 millivolts
2. Neurons	:	-70 millivolts
3. Nodal fibers of cardiac muscles	:	-55 to -60 millivolts
4. Cardiac muscles (Venticular muscle fibers)	:	-85 to -90 millivolts
5. Visceral smooth muscles	:	-50 millivolts
6. Skeletal muscles	:	-85 to -90 millivolts.

Action Potential

Definition : An action potential is a rapid change in the membrane potential followed by a return to the resting membrane potential.

Stages of action potential :

a. Resting stage
b. Depolarization stage
c. Repolarization stage
d. Spike potential
e. Negative after potential
f. Positive after potential or hyperpolarization.

The successive stages of action potential are :

1. *Resting stage :* This is the resting membrane potential before the action potential begins. The membrane is said to be 'polarized' during this stage because of the very large negative membrane potential that is present.
2. *Depolarization stage :* When the negetivity of the membrane potential rises rapidly in positive direction due to influx (enter) of sodium ions is called dedpolarization.
3. *Repolarization stage :* Immediately after depolarization (within a few 10,000ths of a seccond) the negetivity of the membrane potential re-establishes towards the normal negative resting membrane potential due to efflux of K^+. This is called the *repolarization* of the membrane.
4. *Spike potential* : Initially, the depolarization wave over shoots the zero line and then sharply falls. This sharp rise of the depolarization wave and the rapid fall of repolarization wave is called spike potential.

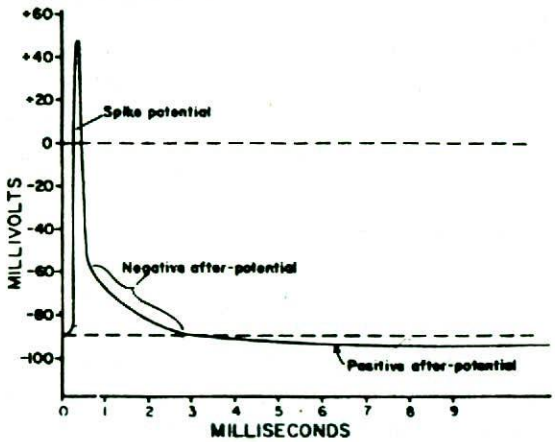


Fig 1-8 . *An ideal action potential*

5. *Negative after Potential :* At the termination of spike potential, the membrane potential sometimes fails to reach the normal resting stage. This is called negative after potential.

   It is believed that sometimes, the concentration of K^+ outside the membrane increases which prevents flow of K^+ from inside to outside. This then prevents the return of membrane potential towards normal.

6. *Positive after potential or hyperpolarization :* Sometimes the negativity of membrane potential become more than its normal level. This is called positive after potential. It is due to excess permeability of membrane to the K^+ at the end of spike potential.

(Ref. Guyton & Hall-11th Edition; page-61 & others)

Refractory period

i. *Definition* : It is the period of action potential during which no action potential is generated in same fiber for another stimulus. It has two parts :

ii. *Parts of refractory peroid* :

   a. *Absolute refractory period (ARP)* : It is the period during which no action potential is developed in previously activated fiber by any strong stimulus.

   b. *Relative refractory period (RRP)* : In this period an action potential may develop by a strong stimulus.

Saltatory conduction

Conduction in myelinated axons depends upon a similar pattern of circular current flow. However, myelin is an effective insulator, and current flow through it is negligible. Instead, depolarization in myelinated axons jumps from one node of Ranvier to the next, with the current sink at the active node serving to electrotonically depolarize to the firing level the node ahead of the action potential. This jumping of depolarization from node to node is called *saltatory conduction*.

It is a rapid process, and myelinated axons conduct up to 50 times faster than the fastest unmyelinated fibers.

(Ref. Ganong 22th edition; page-57)

Orthodromic & Antidromic conduction

An axon can conduct in either direction. When an action potential is initiated in the middle of it, two impulses traveling in opposite directions are set up by electrotonic depolarization on either side of the initial current sink.

In a living animal, impulses normally pass in one direction only, ie, from synaptic junctions or receptors along axons to their termination. Such conduction is called ***orthodromic***. Conduction in the opposite direction is called ***antidromic***. Since synapses, unlike axons, permit conduction in one direction only, any antidromic impulses that are set up fail to pass the first synapse they encounter and die out at that point.

(Ref. Ganong 22th edition; Page-57)

Propagation of action potential

Normally, a resting nerve fibre remains in polarized state, with positive charges lined up along the membrane and negative charges along the inside.

As soon as the fibre is excited, at the point of excitation the polarity is reversed due to increases permeability of Na^+ to the membrane and causes depolarization of the membrane. A local circuit of current flows between the depolarized area and resting area of the membrane; positive current flows inward through the depolarized membrane and outward through. This local depolarization current then excites the adjacent portions of the membrane producing progressively more and more depolarization. The depolarization wave travels in all direction along the entire length of the nerve fibre.

(Ref. Guyton & Hall-11th edition; Page-65,66)

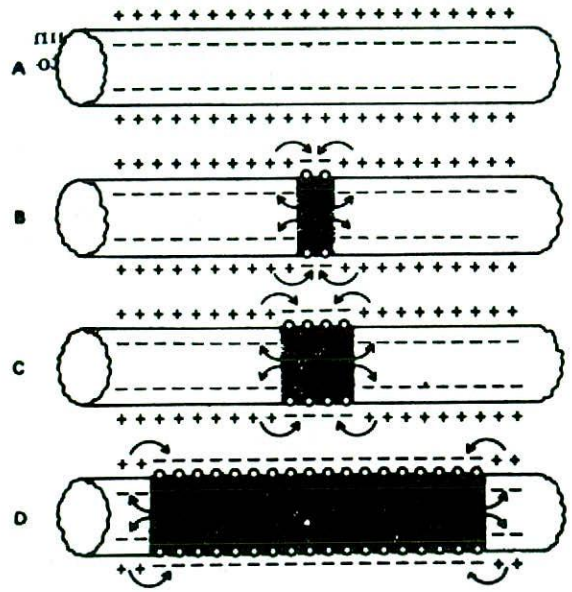


Fig. 1-9. *Propagation of action potential.*

Direction of propagation : An excitable membrane has no single direction of propagation, but the action potential travels in all directions away from the stimulus-even along all branches of a nerve fiber-until the entire membrane has become depolarized.

(Ref. Guyton 11th edition; Page-66)

All-or-nothing principle : Once an action potential has been elicited at any point on the membrane of a normal fiber, the depolarization process travels over the entire membrane if conditions are right, or it does not travel at all if conditions are not right. This is called the *all-or-nothing principle*, and it applies to all normal excitable tissues. Occasionally, the action potential reaches a point on the membrane at which it does not generate sufficient voltage to stimulate the next area of the membrane. When this occurs, the spread of depolarization stops. Therefore, for continued propagation of an impulse to occur, the ratio of action potential to threshold for excitation must at all times be greater than 1. This 'greater than 1' requirement called the ***safety factor for propagation***.

(Ref. Guyton & Hall-11th edition; Page-66)

Nerve Impulse : The process of transmission of depolarization wave along a nerve fibre is called nerve impulse.

Action Potential of Nerve cell

Resting membrane potential of a neuron is usually about -70 mV. A slight decrease in resting membrane potential leads to increased K^+ efflux and Cl^- influx restoring the resting membrane potential. However, when depolarization exceeds 7 mV, the voltage-gated Na^+ channels start to open at an increased rate (Na^+ channel activation), and when the firing level is reached, the influx of Na^+ along its inwardly directed concentration and electrical gradients is so great that it temporarily swamps the repolarizing forces.

The increase in Na^+ conductance is short-lived. The Na^+ channels rapidly enter a closed state called the inactivated state and remain in this state for a few milliseconds before returning to the resting state. In addition, the direction of the electrical gradient for Na^+ is reversed during the over shoot because the membrane potential is reversed, and this limits Na^+ influx. A third factor producing repolarization is the opening of voltage-gated K^+ channels. This opening is slower and more prolonged than the opening of the Na^+ conductance. The net movement of positive charge out of the cell due to K^+ efflux at this time helps complete the process of repolarization. The slow return of the K^+ channels to the closed state also explains the after-hyperpolarization.

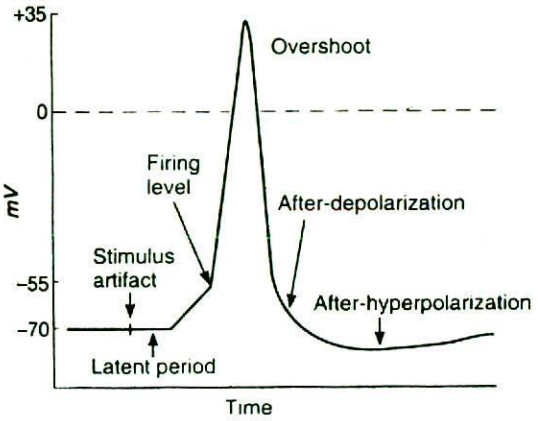


Fig. 1-10. *Action potential in neuron.*

Althogh Na^+ enters the nerve cell and K^+ leaves it during the action potential, the number of ions involved is minute relative to the total numbers present. The fact that the nerve gains Na^+ and loses K^+ during activity has been demonstrated experimentally, but significant differences in ion concentrations can be measured only after prolonged, repeated stimulation.

The slower opening and delayed closing of the voltage-gated K^+ channels also explain accommodation. If depolarization occurs rapidly, the opening of the Na^+ channels overwhelms the repolarizing forces, but if the induced depolarization is produced slowly, the opening of K^+ channels balances the gradual opening of Na^+ channels, and an action potential does not occur.

A decrease in extracellular Ca^{++} concentration increases the excitability of nerve and muscle cells by decreasing the amount of depolarization necessary to initiate the changes in the Na^+ and K^+ conductance that produce the action potential. Conversely an increase in extracellular Ca^{++} concentration stabilizes the membrane by decreasing excitability.

(Ref. Ganong 22th Edition)

Action potential in nerve fibre :

1. *Resting stage :* This is the resting membrane potential before the action potential begins. The membrane is said to be 'polarized' during this stage because of the -90 millivolts negative membrane potential that is present.
2. *Depolarization stage :* At this time, the membrane suddenly becomes very permeable to sodium ions, allowing tremendous numbers of positively charged sodium ions to flow to the interior of the axon. The normal polarized state of -90 millivolts is immediately neutralized by the inflowing sodium ions, with the potential rising rapidly in the positive direction. This is called depolarization.

   In large nerve fibres, the membrane potential actully 'overshoots' beyond the zero level and becomes somewhat positive, but *in some smaller fibers* as well as many central system neurons, the potential merely approaches the zero level and does not overshoot to the positive state.
3. *Repolarization Stage :* Within a few 10,000ths of a seccond after the membrane becomes highly permeable to sodium ions, the sodium channels begin to close and the potassium channels open more than they normally do. Then, rapid diffusion of potassium ions to the exterior re-establishes the normal negative resting membrane potential. This is called the *repolarization* of the membrane.

(Ref. Guyton 10th page-56)

Skeletal Muscle Action Potential

Almost everything regarding initiation and conduction of action potentials in nerve fibers applies equally well to skeletal muscle fibers except for quantitative differences. Some of the quantitative aspects of muscle potentials are the following :

1. Resting membrane potential : about -85 to -90 millivolts in skeletal fibers, the same as in large myelinated nerve fibers.
2. Duration of action potential : 1 to 5 milliseconds in skeletal muscle, about five times as long as large myelinated nerves.
3. Velocity of conduction : 3 to 5 m/sec, about 1/18 the velocity of conduction in the large myelinated nerve fibers that excite skeletal muscle.

Spread of the action potential to the interior of the muscle fiber by way of the transvers tubule system : The skeletal muscle fiber is so large that action potentials spreading along its surface membrane cause almost no current flow deep within the fiber. To cause contraction, these electrical currents must penetrate to

the vicinity of all the separate myofibrils. This is achieved by transmission of the action potentials along transverse tubules (T tubules) that penetrate all the way through the muscle fiber from one side to the other. The T tubule action potentials in turn cause the sarcoplasmic reticulum to release calcium ions in the immediate vicinity of all the myofibrils, and these calcium ions

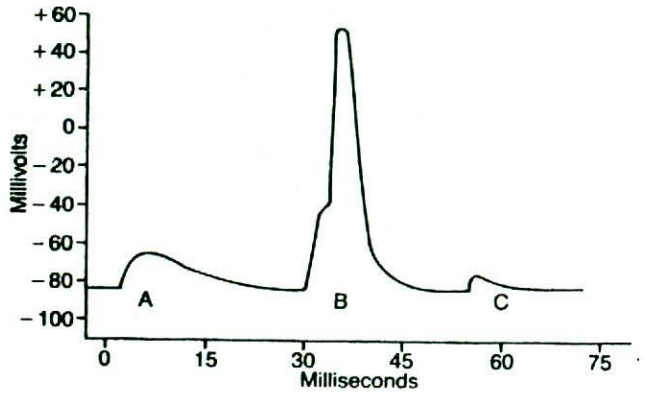


Fig : 1-11. End plate potentials. A, Weakened end plate potential recorded in a curarized muscle, too weak to elicit an action potential; B, normal end plate potential eliciting a muscle action potential. and C, weakened end plate potential.

then cause contraction. This over all process is called excitation-contraction coupling.

Visceral Smooth Muscle Action Potential

Electrical & mechanical activity : Visceral smooth muscle is characterized by the instability of its membrane potential and by the fact that it shows continuous, irregular contractions that are independent of its nerve supply. This maintained state of partial contraction is called tonus or tone. The membrane potential has no true "resting" value, being relatively low when the tissue is active and higher when it is inhibited, but in periods of relative quiescence it averages about -50 mV. Superimposed on the membrane potential are waves of various types . There are slow sine wave-like fluctuations a few millivolts in magnitude and spikes that somethimes overshoot the zero potential line and sometimes do not. In many tissues, the spikes have a duration of

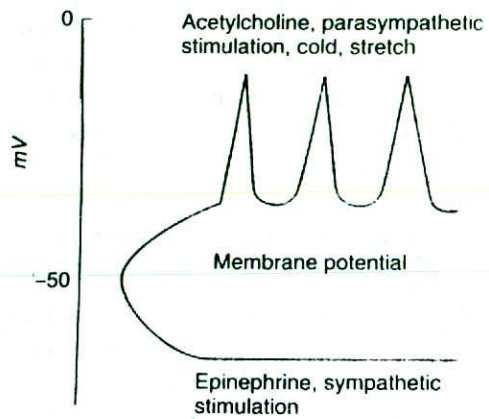


Fig 1-12. Effects of various agents on the membrane potential of intestinal smooth muscle.

about 50 ms. However, in some tissues the action potentials have a prolonged plateau during repolarization, like the action potentials in cardiac muscle. The spikes may occur on the rising or falling phases of the sine wave oscillations. There are, in addition, pacemaker potentials similar to those found in the cardiac pacemakers. However, in visceral smooth muscle, these potentials are generated in multiple foci that shift from place to place. Spikes generated in the pacemaker foci are conducted for some distance in the muscle. Becasue of the continuous activity, it is difficult to study the relation between the electrical and mechanical events in visceral smooth muscle, but in some relatively inactive preparations, a single spike can be generated. The muscle starts to contract about 200 ms after the start of the spike and 150 ms after the spike is over. The peak contraction is reached as long as 500 ms after the spike. Thus, the excitation-contraction coupling in visceral smooth muscle is a very slow process compared with that in skeletal and cardiac muscle, in which the time from initial depolarization to initiation of contraction is less than 10 ms.

(Ref. Ganong 22th Edition; Page-82)

Cardiac ion channels :

i. *Voltage-gated channels*
   - Na^+
   - TCa^{++}
   - LCa^{++}
   - K^+
   - Inward rectifying
   - Delayed rectifying
   - Transient outward

ii. *Ligand-gated K^+ channels :*
   - Ca^+ activated
   - Na^+ activated
   - ATP-sensitive
   - Acetylcholine-activated
   - Arachidonic acid-activated.

(Ref. Ganong 21th edition, Page 80)

Cardiac Muscle Action potential

Resting membrane & action potentials : The resting membrane potential of individual mammalian cardiac muscle cells is about -90 mV (interior negative to exterior). Stimulation produces a propagated action potential that is responsible for initiating contraction.

Depolarization proceeds rapidly, and an overshoot is present, as in skeletal muscle and nerve. But this is followed by a *plateau* before the membrane potential returns to the baseline. In mammalian hearts, depolarization lasts about 2 ms, but the plateau phase and repolarization last 200 ms or more. Repolarization is therefore not complete until the contraction is half over. With extracellular recording, the electrical events include a spike and a later wave that resemble the QRS complex and T wave of the ECG.

As in other excitable tissues, changes in the external K^+ concentration affect the resting membrane potential of cardiac muscle, whereas changes in the external Na^+ concentration affect the magnitude of the action potential.

i. The initial rapid *depolarization* and the overshoot *(phase 0)* are due to opening of voltage-gated Na^+ channels similar to that occurring in nerve and skeletal muscle.

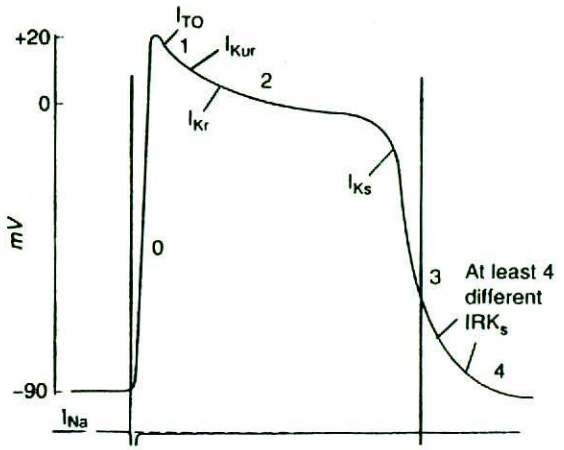


Fig: 1-13. Phases of the action potential of a cardiac muscle fiber. 0, depolarization due to rapid influx of Na+ ions; 1, initial rapid repolarization due to closure of Na channels; 2, plateauphase due to slow influx of Na+ and Ca++ through the slow Na+-Ca++ channels; 3, late rapid repolarizaion due to eflux of K+ ions; 4, base line.

ii. The initial rapid *repolarization (phase 1)* is due to closure of Na^+ channels.

iii. The *subsequent prolonged plateau (phase 2)* is due to a slower but prolonged opening of voltage-gated Ca^{2+} channels.

iv. Final repolarization *(phase 3)* to the resting membrane potential *(phase 4)* is due to closure of the Ca^{2+} channels and K^+ efflux through various types of K^+ channels.

The voltage-gated Na^+ channel in cardiac muscle has two gates an outer gate that opens at the start of depolarization, at a membrane potential of -70 to -80 mV; and an inner gate that then closes and precludes further influx until the action potential is over (Na^+ channel inactivation).

The slow Ca^{2+} channel is activated at a membrane potential of -30 to -40 mV.

There are three types of K^+ channels that produce repolarization. The *first* produces a transient, early outward current (I_{TO}) that produces an early incomplete repolarization. The *second* is inwardly rectifying ie, at plateau potentials it allows K^+ influx but resists K^+ efflux, and only at lower membrane potentials does it permit K^+ efflux. The current it produces is called I_{Kr}. The *third* type is a slowly activating (delayed rectifying) type that produces a current called I_{Ks}. The sum of I_{Kr} and I_{Ks} is a small net outward current that increases with time and *produces repolarization.*

N.B. In cardiac muscle, the repolarization time decreases as the cardiac rate increases.

(Ref. Ganong 22th Edition; Page-78,80)

Nodal fibers of cardiac muscle action potential

Mechanism of Sinus Nodal Rhythmicity : The potential of the sinus nodal fiber between discharges has a negativity of only -55 to -60 millivolts in comparison with -85 to -90 millivolts for the ventricular muscle fiber. The cause of this reduced negativity is that the cell membranes of the sinus fibers are naturally leaky to sodium ions. At this level of negativity, the fast sodium channels have mainly become "inactivated," which means that they have become blocked.

Self-Excitation of Sinus Nodal Fibers : Because of the high sodium ion concentration in the extracellular fluid as well as the negative electrical charge inside the resting sinus nodal fibers, the positive sodium ions outside the fibers even normally tend to leak to the inside. Furthermore, the resting nodal fibers have a moderate number of channels that are already open to the sodium ions. Therefore, influx of positively charged sodium ions causes a rising membrane potential. When it reaches a threshold voltage of about -40 millivolts, the calcium-sodium channels become activated, leading to rapid entry of both calcium and sodium ions, thus causing the action potential.

Then the calcium-sodium channels become inactivated (that is, they close) within about 100 to 150 milliseconds after opening, and at about the same time, greatly increased numbers of potassium channels open. Therefore, the influx of calcium and sodium ions through the calcium-sodium channels ceases, while at the same time large quantities of positive potassium ions diffuse out of the fiber, thus terminating the action potential. Furthermore, the potassium channels remain open for another few tenths of a second, carrying a great excess of positive potassium charges out of the cell, which temporarily causes considerable excess negativity inside the fiber; this is called hyperpolarization. This hyperpolarization initially carries the

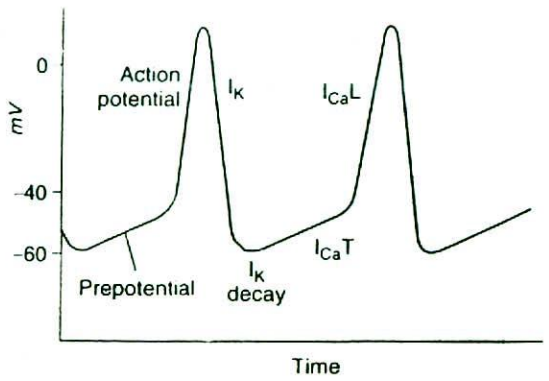


Fig: 1-14. Rhythmical discharge of a sinus nodal fiber. Also, the sinus nodal action potential is compared with that of a ventricular muscle fiber.

"resting" membrane potential down to about -55 to -60 millivolts at the termination of the action potential.

During the next few tenths of a second after the action potential is over, progressively more and more of the potassium channels begin to close. Now the inward-leaking sodium ions once again over balance the outward flux of potassium ions, which causes the "resting" potential to drift upward once more, finally reaching the threshold level for discharge at a potential of about -40 millivolts. Then the entire process begins again: self-excitation, recovery from the action potential, hyperpolarization after the action potentials is over, drift of the "resting" potential again to threshold, then re-excitation again to elicit another cycle. This process continues indefinitely throughout a person's life.

(Ref. Guyton 11th Edition; Page-117, 118)

Skeletal Muscle

All skeletal muscles are composed of numerous fibers ranging from 10 to 80 micrometers in diameter.

Skeletal Muscle Fibre : Each muscle fibre is a single cell, multinucleated; long and cylindrical in shape, and no syncytial bridges between cells. Each fibre is made up of the following successively smaller sub unit-

1. *Sarcolemma :* It is the cell membrane of the muscle fibre. The sarcolemma consist of a true cell membrane, called the *plasma membrane*, and an outer coat consisting of a thin layer of polysaccharide material containing numerous thin collagen fibrillae.
2. *Myofibrils :* Each muscle fibre contains several hundred to several thousand myofibrils. Each fibrils is made by myosin filament and actin filaments, which are large polymarized protein molecule that are responsible for muscle contraction. The myosin and actin filaments partially interdigitate and thus cause the myofibrils to have alternate light and dark band. The light band which contain only actin filaments, are called ***I band*** because they are isotropic to polarized light. The dark band, which contain the myosin filament as well as the end of the actin filament where they overlap the myosin, are called ***A band*** because they are anisotropic to polarized light. The actin filament are attached to ***Z disc.*** The portion of myofibrils that lies between two successive Z discs is called a ***sarcomere*** which is capable of generating its greatest force of contraction.
3. *Sarcoplasm :* The myofibrils are suspended inside the muscle fibre in a matrix called sarcoplasm. The fluid of the sarcoplasm contains large quantities of K, Mg, PO_4, proteins, enzymes and tremendous numbers of mitochondria that lie between and parallel to the myofibrils.

(Ref. Guyton & Hall-11th Edition; Page-72)

Myosin Filament

The myosin filament is composed of multiple myosin molecules, each having a molecular weight of about 480,000. The myosin molecule is composed of six polypeptide chains, two heavy chains and four light chains.

The two heavy chains coil around each other to form a double helix. One end of the each of these chains is folded into a globular protein mass called the myosin head. Thus there are two free heads lying side by side at one end of the double helix myosin molecule; the other end of the coiled helix is called the tail. The four light chains are also parts of the myosin heads, two to each head. The four light chains help control the function of the head during the process of muscle contraction.

(Ref. Guyton & Hall-11th Edition; Page-72)

Actin Filament

The actin filament is composed of three different component-actin, tropomyosin, and troponin.

The actin filament is a double stranded F-actin protein

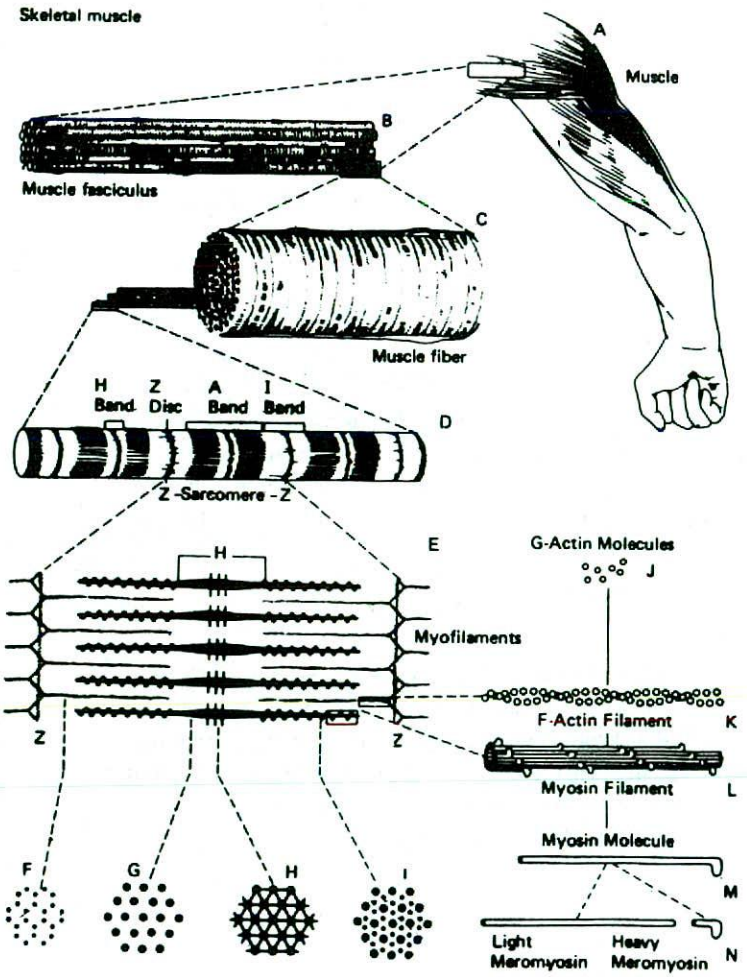


Fig.1-15. Organization of skeletal muscle from gross to the molecular level

molecule. Each strand of the double F-actin helix is composed of polymerized G-actin molecule.

The tropomyosin strand is loosely attached to an F-actin strand and that in a resting state it physically covers the active sites of the actin strands so that interaction can not occur between the actin and myosin to cause contraction.

The ***troponin*** is a complex of three globular protein molecule attached approximately two thirds the distance along each tropomyosin molecule. One of the globular protein (*troponin I*) has a strong affinity for actin, another (*troponin T*) for tropomyosin and a third (*troponin C*) for calcium ions.

(Ref. Guyton 11th Edition)

Mechenism of contraction of skeletal Muscle

Steps in skeletal muscle contraction :

1. Discharge of motor neuron.
2. Release of transmitter (acetylcholine) at motor end plate.
3. Binding of acetylcholine to acetylcholine receptor.
4. Increased Na^+ and K^+ conductance in end plate membrane.
5. Generation of end plate potential.
6. Generation of action potential in muscle fibers.
7. Inward spread of depolarization along T tubules.
8. Release of Ca^{++} from terminal cisterns of sarcoplasmic reticulum and diffusion to thick and thin filaments.
9. Binding of Ca^{++} to troponin C, uncovering myosin binding sites on actin.
10. Formation of cross linkages between actin and myosin and sliding of thin on thick filaments, producing shortening.

(Ref. Ganong 22th Edition; page-70)

Mechenism of relaxation of skeletal Muscle

1. Ca^{++} pumped back into sarcoplasmic reticulum.
2. Release of Ca^{++} from troponin.
3. Cessation of interaction between actin and myosin.

(Ref. Ganong 22th Edition; page-70)

Sliding filament theory of muscle contraction

Mechenism :

a. There is no shortening, thickening, or folding of the individual filaments.
   i. A band remains constant in size
   ii. H zone becomes denser
   iii. I band varies in length becoming shorter.
b. *As a muscle contracts* :
   i. Z lines come closer together
   ii. The width of the I bands decreases
   iii. The width of the H zones decreases
   iv. But, there is no change in the width of the A band.
c. Conversely, *as a muscle is stretched*, the width of the I bands and H zones increases, but there is still no change in the width of the A band.

Excitation & contraction coupling

i. *Excitation & contraction coupling involves four steps* :
   a. The propagation of action potential into the T-tubule and release of Ca^+ from the terminal cisternae
   b. The activation of muscle by Ca^{++}
   c. The generation of tension by the muscle proteins
   d. The relaxation of the muscle.

ii. *Mechanism* : Calcium ions (Ca^{++}) link action potentials in a muscle fibre to contraction.
   a. In resting muscle fibres, Ca^{++} is stored in the endoplasmic (sarcoplasmic) reticulum.
   b. The tubules of the T system terminate near the calcium-filled sacs of the sarcoplasmic reticulum.
   c. Each action potential created at the neuromuscular junction sweeps quickly along the sarcolema and is carried into the T system.
   d. The arrival of the action potential at the ends of the T system triggers the release of Ca^{++}.
   e. The Ca^{++} diffuses among the thick and thin filaments where it binds to troponin on the thin filaments.
   f. This turns on the interaction between actin and myosin and the sarcomere contracts.
   g. Because of the speed of the action potential (milliseconds) the action potential arrives virtually simultaneously at the ends of all the tubules of the T system, ensuring that all sarcomeres contract in unison.

When the process is over, the calcium is pumped back into the sarcoplasmic reticulum using a Ca^{++} ATPase.

Role of calcium in muscle contraction

Action potential along T-tubules
↓
Ca^{++} released fromterminal cisternae of sarcoplasmic reticulum
↓
Ca^{++} ions binds with troponin C
↓
Inhibition of troponin-tropomyosin complex
↓
Uncovers the active sites of the actin
↓
Interaction of actin and myosin
↓
Muscle contraction.

Muscle twitch

i. *Definition* : A single action potential causing a brief contraction followed by relaxation is called muscle twitch.
ii. *Duration* :
   a. Fast muscle fibre : 7.5 milli seconds
   b. Slow muscle fibre : 100 milli seconds.

Rigor mortis

i. *Definition* : The stiffness of muscle after death is called rigor mortis. It usually starts 2-3 hours after death.

ii. *Duration* : It remains up to 36 hours after death.

iii. *Mechenism* : It is due to destruction of all ATP and phosphorylcreatine after death. ATP is required to cause separation of cross bridges from actin filaments. If no ATP is available the actin-myosin complex become stable; this accounts for the extreme muscular rigidity (rigor mortis).

Muscle tetanization

i. *Definition* : It is a condition in which the successive contractions fuse together and cannot be distinguished one from the other.

ii. *Mechenism* : The process of contracting takes some 50 millisecond and relaxation of the fiber takes another 50-100 millisecond. Because the refractory period is so much shorter than the time needed for contraction and relaxation, the fibre can be maintained in the contracted state so long as it is stimulated frequently enough i.e 50 stimuli per second. Such sustained contraction is called *tetanus*.

Sequence of events in contraction and relaxation of visceral smooth muscle :

1. Binding of acetylcholine to muscarinic receptors.
2. Increased influx of Ca^{++} into the cell.
3. Activation of calmodulin dependent myosin light chain kinase.
4. Phosphorylation of myosin
5. Increased myosin ATPase activity and binding of myosin to actin.
6. Contraction.
7. Dephosphorylation of myosin by various phosphatases.
8. *Relaxation*, or sustained contaction due to the latch bridge mechanisms.

(Ref. Ganong 21th Edition; page-84)

Motor Unit

All the muscle fibres innervated by a single motor nerve fibre are called a motor unit.

Autonomic Nervous System

Division and root value :

Autonomic nervous system divides into-

1. Sympathetic nervous system.
2. Parasympathetic nervous system.
    1. *Sympathetic nervous system :* Originates in the spinal cord between the segments of T_1 and L_2 or thoraco-lumbar out flow.
    2. *Parasympathetic nervous system :* Originates as cranio-sacral out flow. The cranial nerves are III, VII, IX and X. The spinal verves are S_2 to S_4.

Synthesis of acetylcholine

Acetylcholine is synthesized in the body by the interaction of acetylCoA and Choline in the presence of enzyme choline acetyl transferase. The aeetyl CoA comes from acetic acid and CoASH in presence of ATP and enzyme acetyl thiokinase.

Acetic acid + CoA SH $\xrightarrow{\text{Acetyl thiokinase}}$ Acetyl CoA

AcetylCoA+Choline $\xrightarrow{\text{Choline acetyltransferase}}$ Acetyl choline.

(Ref.Guyton 11th Edition; Page-751)

Synthesis of norepinephrine and epinephrine :

The basic steps of norepinephrine and epinephrine synthesis are-

1. At first amino acid tyrosin is actively transported from the circulation into the axoplasm of terminal ending of sympathetic nerve fibres.
2. Tyrosin $\xrightarrow{\text{Hydroxylation (Hydroxylase)}}$ DOPA
3. DOPA $\xrightarrow{\text{Decarboxylation (Decarboxylase)}}$ Dopamine
4. Transport of dopamine inside the chromaffin vesicles.
5. Dopamine $\xrightarrow{\text{Hydroxylation (Hydroxylase)}}$ Nor-epinephrine

In the adrenal medulla, this reaction goes still one step further to transform about 80 percent of the norepinephrine into epinephrine, as follows :

6. Nor-epinephrine $\xrightarrow{\text{Methylation (N-Methyltransferase)}}$ Epinephrine.

(Ref. Guyton 11th Edition; Page 751)

Cholenergic receptors

A. *Necotinic receptors* :: Located in the synapse between the pre and post ganglionic neurones of both sympathetic and parasympathetic system. It is so called because its function is that of nicotine.

B. *Muscarinic receptors :* Found in all the effector cells stimulated by the post ganglionic neurones of the parasympathetic nervous system. It is so called because it collect from muscarine, a poisonous substance of fungus.

(Ref. Guyton 11th Edition; Page 752)

Adrenergic receptors

A. Alpha receptors which again divides into α_1 and α_2

B. Beta receptors which also divides into β_1 and β_2.

(Ref. Guyton 11th Edition; Page 752)

Functions of beta receptors :

1. Vasodilatation (β_2)
2. Cardioacceleration (β_1)
3. Increased myocardial strength (β_1)
4. Intestinal relaxation (β_2)

5. Uterus relaxation (β_2)
6. Bronchodilatation (β_2)
7. Calorigenesis (β_2)
8. Glycogenolysis (β_2)
9. Lipolysis (β_1)
10. Bladder wall relaxation (β_2).

(Ref. Guyton 11th Edition; Page-753)

Functions of alpha receptors :

1. Vasoconstriction
2. Iris dilatation
3. Intestinal relaxation
4. Intestinal sphincter contraction
5. Pilomotor contraction
6. Bladder spincter contraction.

(Ref. Guyton 10th Edition; Page-753)

Cyclic AMP

i. *Definition* : cAMP is cyclic adenosine 3',5' monophosphate.

ii. *Formation* : It is formed from ATP by the action of the enzyme *adenylyl cyclase*

iii. *Fate* : It is converted to physiologically inactive 5'-AMP by the action of the enzyme *phosphodiesterase*.

iv. *Mechenism of action* : Cyclic AMP activates one of the cyclic nucleotide dependent protein kinases (*protein kinase A*) that, like protein kinase C, catalyzes the phosphorylation of proteins, changing their conformation and altering their activity.

Example : A typical example is the activation of phosphorylase kinase in the liver by epinephrine via cAMP and protein kinase A.

In addition, the active catalytic subunit of PKA moves to the nucleus and phosphorylates the cAMP-responsive element-binding protein (CREB). This transcription factor then binds to DNA and alters transcription of a number of genes.

v. *Metabolism* : Cyclic AMP is metabolised by a phosphodiesterase. This phosphodiesterase is inhibited by methylxanthines such as caffeine and theophyline; consequently, these compounds augment hormonal and transmitter effects mediated via cAMP.

(Ref. Ganong 22th edition, Page 42)

Q. 00. **Write short notes on- chromosome.**

i. *Definition* : Chromosomes are deeply stained thread like structures within the nucleus of each animal cell.

ii. *Chromosomes number* : 46 or 23 pairs
   a. Autosomes : 22 pairs
   b. Sexchromosomes : 1 pair (XX or XY).

iii. *Structure of chromosome* : Each choromosome is composed of a double helix of DNA along with histone and non-histone proteins. The DNA-protein complex exists as a highly coiled or folded structure.
   a. The *non-histone* proteins are DNA and RNA polymerases, gene regulatory proteins and HMG (high mobility group) proteins.
   b. The *histones* are the most abundant group of basic proteins which help packaging of chromosomal DNA. There are five histone proteins according to the concentration of arginine and lysine residues : H1,H2A, H2B, H3, and H4.

iv. *Function* : Chromosomes act as carries of units of inheritance in the form of genes of nuclear DNA. Genes are borne by the chromosomes in linear series as parts of specific DNA molecules.

DNA

It is a complex protein of high molecular weight consisting of deoxyribose, phosphoric acid, and four bases (2 purines and 2 pyrimidines). DNA is found mainly in the chromosomes of the cell nucleus.

Components of DNA :

i. Sugar : 2-deoxy-D-ribose
ii. Acid moiety : Phosphoric acid
iii. Bases :
   a. Purines : Adenine & Guanine
   b. Pyrimidines : Cytosine & Thymine

Function of DNA :

The genetic information store in the nucleotide sequence of DNA serves two purposes-

i. It is the source of information for the synthesis of all protein molecules of the cell & organism.
ii. It provides the information inherited by daughter cells or offspring.

(Ref. Guyton 11th Edition)

RNA

RNA (Ribonucleic acid) is a polymer of purine & pyrimidine ribonucleotides linked together by 3, 5, - phosphodiaster bridge. RNA is found mainly in the cytoplasm & nucleolus.

Components of RNA :

i. Sugar : D-ribose
ii. Acid moiety : Phosphoric acid
iii. Bases :
   a. Purines : Adenine & Guanine
   b. Pyrimidines : Cytosine & uracil.

Types of RNA :

1. *Messenger RNA (m RNA) :* Which carries the genetic code to the cytoplasm for controlling the formation of the proteins.
2. *Transfer RNA (t RNA) :* Which transports activated amino

Trait	DNA	RNA
1. Bases	1. Adenine, guanine, cytosine and thymine.	1. Adenine, guanine, cytosine and uracil.
2. Sugar moiety	2. Deoxyribose.	2. D-ribose
3. Structure	3. Have 2 strands of antiparallel double helical molecule.	3. Single-stranded molecules.
4. Situation	4. Solely intranuclear and mitrochondrial.	4. Both extra & intranuclear (cytoplasm & nucleolus).
5. Functions	5. i. Carry genetic information from one generation of cells to the next & undergo mutation. ii. Concerned with source of information protein synthesis.	5. i. Carry no genetic information & undergo no mutation. ii. Concerned with protein synthesis.

acids to the ribosomes to be used in assembling the protein molecules.

3. *Ribosomal RNA (r RNA) :* Which along with about 75 different proteins, forms the ribosomes, the physical and chemical structure on which protein molecules are actually assembled.

Functions of RNA : It is involved in protein synthesis.

(Ref. Guyton 11th Edition; Page 31)

Transcription

Assembly of the RNA molecule from activated nucleotides using the DNA strand as a template- the process is called transcription.

(Ref. Guyton & Hall-11th edition; Page-33)

Assembly of the RNA molecule is accomplished by DNA under the influence of the enzyme RNA polymerase.

Translation

The process of formation of proteins on the ribosomes is called translation.

(Ref. Guyton& Hall-1th Edition; page-33)

Aging

i. Introduction : Aging is a general physiologic process that is as yet poorly understood. Life expectancy has increased is due for the most part to improved treatment and prevention of infections and other causes of early death.

ii. *Effects and theories of aging* : Aging affects cells and the systems made up of them, as well as tissue components such as collagen, and numerous theories have been advanced to explain the phenomenon.

a. *One theory of aging* holds that tissues age as a result of random mutations in the DNA of somatic cells, with consequent introduction of cumulative abnormalities.

b. *Others* hold that cumulative abnormalities are produced by increased cross-linkage of collagen and other proteins, possibly as the end result of the nonenzymatic combination of glucose with amino groups on these molecules.

c. *A third theory* envisions aging as the cumulative result of damage to tissues by free radicals formed in them. It is interesting in this regard that species with longer life spans produce more *superoxide dismutase*, an enzyme that inactivates oxygen-free radicals.

iii. *Prolongation of aging* : It is now established that in experimental animals, a chronically decreased caloric intake prolongs life, and this could be true in humans as well. One possible explanation for this effect of *caloric restriction* is decreased metabolism, with decreased formation of protein cross-links and decreased production of free radicals. It may be relevant in this regard that in yeasts, worms, and flies, mutations in the homologs of one of the mammalian insulin pathways causes a dramatic prolongation of their life span. However, the exact cause of the lengthened life span produced by caloric restriction remains to be determined.

iv. *Hormonal effects in aging* : In aging humans, there are declines in the circulating levels of some sex hormones, the adrenal androgen dehydroepiandrosterone and its sulfate, and growth hormone. Replacement therapy with estrogens and progesterone in women decreases the incidence of osteoporosis and heart disease. Replacement therapy with testosterone, dehydroepiandrosterone, and growth hormone each has some salutary effects, but each also has undesirable side effects, and there is little if any evidence that they prolong life.

(Ref. Ganong 22th edition, Page-48, 49)

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Directions : *Write T for true & F for false against* each of the following statement.

Introduction

Q. 01. **Objectives of learning of physiology are**
- T a. to acquire knowledge about the formation of human body.
- T b. to understand the functions of different organs.
- T c. to know the mechanisms of functions.
- T d. to understand the purpose of the function.
- T e. to understand the co-ordination of different organs.

Q. 02. **Human cell**
- T a. provides structural and functional unit
- T b. is bounded by cell membrane
- F c. is composed of bio-molecules only
- F d. forms internal environment
- F e. is a prokaryotic cell.

Q. 03. **Cells are held together by**
- T a. intercellualar supporting structure.
- F b. fusion.
- F c. positive pressure in the interstitium.
- F d. electrostatic force.
- F e. chemical bond.

Q. 04. **Common characteristics of all cells include**
- T a. multiplication.
- T b. energy production.
- T c. energy consumption.
- T d. waste product removal.
- F e. detoxification of toxic substances.

Q. 05. **Structural protein includes**
- T a. contractile protein.
- T b. microtubules.
- T c. collagen fibres.
- F d. transport proteins.
- F e. immunoglobulin.

Q. 06. **Carbohydrate in cell plays important role in**
- T a. nutrition.
- T b. energy storage.
- F c. cellular structure.
- F d. cellular synthetic process.
- F e. enzymatic activity.

Q. 07. ***The normal basal acid output is***
- T b. 5-10 mmol/hr
- F a. 1-2 mmol/hr
- F c. 10-15 mmol/hr
- F d. 20-25 mnol/hr
- F e. 2-5 mnol/hr.

Q. 08. **Which amino acid can proteinate and deproteinate at neutral pH is**
- T a. Histidine
- F b. Serine
- F c. Proline
- F d. Glycine
- F d. Alanine.

Q. 09. **Autoregulation is seen in**
- T a. Muscles
- T b. Kidneys
- T c. Brain
- F d. Liver
- F e. All of the above.

Q. 10. **Cell shape & motility are provided by**
- T a. Microtubules
- F b. Microfilaments
- F c. Golgi apparatus
- F d. Nucleus
- F e. ER.

ECF & ICF

Q. 11. **Total body water (in a subject having 70 kg body wt) is**
- T a. 42 L
- F b. 4200 ml
- F c. 30 L
- F d. 15 L
- F e. 28 L.

Q. 12. **Oedema may be due to**
- T a. increased hydrostatic pressure in the capillary.
- T b. decreased colloidal osmotic pressure.
- F c. decreased hydrostatic pressure in the capillary.
- F d. increased colloidal osmotic pressure.
- F e. decreased lymphatic obstruction.

Q. 13. **ECF contain large amount of**
- T a. Na^+
- T b. Cl^-
- T c. HCO_3^-
- F d. Mg^{++}
- F e. K^+

Q. 14. **Concentration of Na^+ ion outside the cell is**
- T a. 142 mEq/L.
- F b. 145 mEq/L.
- F c. 140 mEq/L
- F d. 100 mEq/L
- F e. 120 mEq/L

Q. 15. **Concentration of K^+ inside the cell is**
- T a. 140 mEq/L
- F b. 15 mEq/L
- F c. 45 mEq/L
- F d. 155 mEq/L
- F e. 150 mEq/L

Q. 16. **Concentration of Cl^- outside the cell is**
- T a. 103 mEq/L
- F b. 15 mEq/L
- F c. 45 mEq/L
- F d. 113 mEq/L
- F e. 123 mEq/L

Q. 17. ***ECF forms what percentage of body weight***
- T a. 25%
- F b. 10%
- F c. 33%
- F d. 60%
- F e. 30%.

Q. 18. **Most diffusible ion in excitable tissue is**
- T a. Cl^-
- F b. Na^+
- F c. K^+
- F d. PO_4^-
- F b. Ca^{++}.

Q. 19. **The majority of body sodium is present in**
- T a. Extracellular fluid
- F a. Bone.
- F c. Intracellular fluid
- F d. Plasma
- F d. Blood.

Q. 20. **Content of Na^+ in ringer lactate is - - meq/L**
- T a. 130
- F b. 154
- F c. 121
- F d. 144
- F c. 115

Q. 21. **Total body sodium in meq/Kg is**
- T a. 58
- F b. 41
- F c. 70.7
- F d. 91.0
- F b. 52

Q. 22. **Plasma sodium concentration is**
- T a. 140 meq/L
- F b. 120 meq/L
- F c. 3.5 meq/L
- F d. 110 meq/L
- F c. 130 meq/L

Q. 23. **Sodium channels are specifically blocked by**
- T a. Tekadotoxin
- F b. Nifedipirie
- F c. Tetra Ethyl Lead
- F d. Choline
- F b. All of the above.

Q. 24. **Potassium is maximum in**
- T a. Plasma
- F b. Cell
- F c. Interstitium
- F d. Bone
- F e. Skin.

Q. 25. **Plasma K constitute what percentage of total body potassium:**
- T a. 0.4%
- F b. 7.6%
- F c. 10.4
- F d. 89.6%
- F e. 1.6%

Q. 26. **If potassium levels are 39 mg% calculate the same in meq/L**
- T a. 10
- F b. 1
- F c. 3.9
- F d. 100
- F e. 13

Q. 27. **Potassium content in colonic secretion is**

T a. 30 meq/L
F b. 10 meq/L
F c. 15 meq/L
F d. 50 meq/L
F e. 45 meq/L.

Q. 28. **Which secretion contributes to the maximum amount of potassium**
T a. Salivary
F b. Gastric
F c. Pancreatic
F d. Biliary
F e. Lacrimal.

Q. 29. **Highest concentration of potassium is seen in**
T a. Saliva
F b. Gastric juice
F d. Bile
F d. Pancreatic secretion
F e. Lacrimal.

Q. 30. **What is the useful function of nitrogen in the body?**
T a. Prevents atelectasis
T b. Decreases rate of combustion
T c. Delays alveolar collapse
T d. All of the above
F e. None of the above

Q. 31. **N_2 has a role in body as it**
T a. Prevents atelectesis
F b. Decreases rate of combustion
F c. Delays alveolar collapse
F d. All of the above
F e. None of the above.

Q. 32. **Fluoride ions act by inhibiting**
T a. Enolase
F b. Cytochrome oxidase
F c. Carbonic anhydrase
F d. Hexokinase
F e. None of the above.

Q. 33. **Deficiency of which vitamin is not known in newborns**
T a. E
F b. C
F c. D
F d. K
F e. A

Q. 34. **Highest concentration of vitamin C in the body is found in the**
T a. Adrenal cortex
F b. Liver
F c. Kidney
F d. Spleen.
F d. Gall bladder.

Homeostasis

Q. 35. **Homeostasis means**
T a. keeping relative constancy of internal environment.
F b. stasis of fluid flow.
F c. rapid change of internal environment.
F d. slow change of internal environment.
F e. away from optimal environment.

Q. 36. **The control system in our body includes**
T a. buffer system.
T b. nervous system.
T c. genetic control system.
F d. urogenital system.
F e. integumentary system.

Q. 37. **Principles of control systems are**
T a. negative feed back.
T b. positive feed back.
T c. feed forward feedback.
T d. adaptive feed back.
F e. reflex action.

Q. 38. **Basic regulatory mechanism for intracellular biochemical activities are**
T a. enzyme regulation.
T b. genetic regulation.
F c. nervous regulation.
F d. hormone regulation.
F e. metabolic regulation.

Q. 39. **Negative feed back means**
T a. center sending negative signal to appropriate organ.
T b. a reversible phenomenon.
T c. opposite of initiating signal.
F d. center receiving negative information from periphey.
F e. acceleration of initiating factor.

Q. 40. **Sickness of a cell results from**
T b. moderate dysfuncition.
T e. cellular injury.
F a. mild dysfunction.
F c. extreme dysfunction.
F d. loss of all fucntion.

Q. 41. **Increased blood osmolality**
T a. can occur as a result of dehydration.
T d. may cause cellular dehydration.
F b. causes decreased blood osmotic pressure.

F c. is accompanied by a lower ADH level.
F e. can produce oedema.

Cell membrane

Q. 42. **Cell membrane**
T a. maintains the intracellular environment
T b. contains receptor protein and ion channel.
F c. separates blood from extracellular fluid.
F d. is composed of organic and inorganic substances.
F e. serves as a defensive layer against invasion of foreign particle.

Q. 43. **Lipid barriers of cell membrane**
T a. prevent passage of water soluble substances
T b. are fluid in nature
T c. are consist of hydrophilic and hydrophobic region
F d. do not allow passage of N_2, O_2, CO_2
F e. are composed of phospholipid only

Q. 44. **Membrane protein acts as**
T a. structural element
T b. transporter of molecules
T c. an enzyme
F d. normal metabolic fuel
F e. cellular defense system

Q. 45. **Integral proteins acts as**
T a. transporters of ions.
T b. enzymes.
F c. transporters of water.
F d. transporters of lipids.
F e. receptors for antigen.

Q. 46. **Cells are bordered at their surface by**
T a. plasma membrane.
F b. a layer of protein.
F c. layer of carbohydrate.
F d. layer of lipid.
F e. cell wall.

Q. 47. **Receptors proteins are found in**
T a. the cell membrane.
T b. cytosol.
F c. nucleus.
F d. endoplasmic reticulum.
F e. golgi apparatus.

Q. 48. **On weight basis, the membrane contains protein and lipid in the ratio of**
T a. 2:1
F b. 1:2
F c. 1:1
F d. 4:1
F e. 2:3

Cell organalles

Q. 49. **The discrete functional parts of a cell are called**
T a. organelles.
F b. molecule.
F c. ions.
F d. organs.
F e. membrane.

Q. 50. **The organelle that contains digestive enzyme are**
T a. lysosomes.
F b. mitochondria.
F c. peroxisomes.
F d. endoplasmic reticulum.
F e. golgi apparatus.

Q. 51. **Cellular digestive function is served by**
T a. lysosome
F b. mitochondria
F c. golgi apparatus
F d. nucleus
F e. ribosome

Q. 52. **Protein packaging and vesicle forming organelles are :**
T a. golgi apparatus.
F b. rough endoplasmic reticulum.
F c. smooth endoplasmic reticulum.
F d. ribosome.
F e. lysosome.

Q. 53. **Organelle containing hydrolytic enzymes is :**
T a. lysosome.
F b. mitochondrion.
F c. endoplasmic reticulum.
F d. golgi apparatus.
F e. peroxisome.

Q. 54. **The organelles that store intracellular Ca^{++} are :**
T a. endoplasmic reticulum.
T b. mitochondria.
F c. ribosome.
F d. golgi apparatus.
F e. lysosome.

Q. 55. **The network of dividing and uniting channels distributed in cytoplasm is known as**
T a. endoplasmic reticulum.
F b. cytoskeleton.
F c. microtrabecular lattice.

F d. intracellular network.
F e. fibrin network.

Q. 56. **Ribosome synthesizes**
T a. proteins.
F b. nucleic acid.
F c. aminoacids.
F d. sugars.
F e. ATP.

Q. 57. **Ribosomes are**
T a. composed of proteins and RNA.
T b. the site of protein synthesis.
T c. granular particles.
F d. membranous organelles.
F e. associated with smooth endoplasmic reticulum.

Q. 58. **Ribosome is made up of**
T a. protein.
T b. RNA.
F c. phospholipid.
F d. steroid hormones.
F e. cholesterol.

Q. 59. **Lysosome has enzymes namely**
T a. ribonuclease.
T b. cathepsins.
T c. deoxyribonuclease.
F b. glycosides.
F e. phosphate esters.

Q. 60. **Lysosomal enzymes are**
T a. ribonuclease.
T b. cathepsins.
T c. deoxyribonuclease.
F d. phosphate esters.
F e. glycosides.

Q. 61. **Lysosomes**
T a. are membrane bound structure.
T b. can cause inflammation.
T c. are formed by Golgi apparatus.
T d. may form phagosome.
F e. originates from nucleosome.

Q. 62. **Peroxisomes originates from**
T a. smooth endoplasmic reticulum.
F b. golgi apparatus.
F c. rough endoplasmic reticulum.
F d. mitochondrial membrane.
F e. cell membrane.

Q. 63. **Mitochondrion**
T a. stores Ca^{++} ion.
T b. has its own DNA.
T c. is a chemical power plant.
F d. is round shaped organelle.
F e. contains proteolytic enzyme.

Q. 64. **Regarding endoplasmic reticulum**
T a. in muscle they are termed as sarcoplasmic reticulum.
T b. it is a cytoplasmic membranous organelle.
F c. the smooth endoplasmic reticulum is concerned with protein synthesis.
F d. the rough endoplasmic reticulum is concerned with lipid synthesis.
F e. the ribosomes are attached with smooth endoplas mic reticulum.

Q. 65. **The human cell nucleus**
T a. has a skeleton of five filaments.
T b. is necessary for cell division.
T c. has a membrane which is permeable to nucleic acid.
F d. in somatic cell contains 44 chromosomes.
F e. stores genetic materials in the nucleolus.

Q. 66. **Secretory vesicles are important store for**
T a. protein hormones.
T b. extracellular enzyme.
F c. intracellular enzyme.
F d. steroid hormone.
F e. ATP.

Q. 67. **Vesicle**
T a. is a membrane bound sac.
T b. transports large molecules.
F c. transports ions.
F d. transports substances following concentration gradient.
F e. can traverse the cell membrane.

Q. 68. **Receptors proteins are found in**
T a. cytosol.
T b. the cell membrane.
F c. nucleus.
F d. endoplasmic reticulum.
F e. golgi apparatus.

Q. 69. **Nissl's substance is composed of**
T a. Rough endoplasmic reticulum
F b. Nerve cell vesicles
F c. Aggregated mitochondria
F d. Deposits of pigmented granules
F c. Mitochondria.

Q. 70. **Marker of Golgi apparatus**
T a. Galactosyl transferase
F b. Acetyl CoA synthase

F c. Pyruvate kinase
F d. Malonyl Co A
F d. Lactate dehydrogenase.

Membrane trnasport

Q. 71. **Transport mechanisms for large particle through the cell membrane are**
T a. exocytosis.
T b. pinocytosis.
F c. osmosis.
F d. primary active transport.
F e. facilitated diffusion.

Q. 72. **Ionized calcium is**
T a. required for coagulation of blood.
T b. needed for contraction of muscle.
T c. required for neuromuscular transmission.
T d. present in sarcoplasmic reticulum.
F e. required for relaxation of muscle.

Q. 73. **The cell obtains nutrients and other substances from the surrounding fluid by means of**
T a. pump.
T b. ingestion of small vesicle that contain ECF.
T c. ingestion of large particles.
F d. limited molecular movement.
F e. a process called exocytosis.

Q. 74. **Processes for difusion of vesicle with cell membrane are :**
T a. Exocytosis.
F b. Pinocytosis.
F c. Endocytosis.
F d. Phagocytosis.
F e. Internalization.

Q. 75. **Processes stopped due to lack of ATP formation are**
T a. overlapping of actin and myosin.
T b. movement of Na^+ out of the cells.
F c. osmosis.
F d. movement of K^+ out of a cell.
F e. exocytosis.

Q. 76. **Substances that can diffuse easily through cell membrane are**
T a. steroid
F b. Na^+
F c. glucose
F d. protein
F e. insulin.

Q. 77. **The rate of diffusion of a particle across a membrane will increase if**
T a. the concentration gradient of the particles increase.
T b. the lipid solubility of the particle increases.
F c. the area of the membrane decreases.
F d. the thickness of the membrane increases.
F e. the size of the particle increases.

Q. 78. **With regard to osmosis across the cell membrane**
T a. increased intracellular hydrostatic pressure would help to oppose osmotic swelling.
T b. water moves along its own concentration gradient.
T c. cells will swell in hypotonic solution.
F d. increased extra cellular hydorstratic pressure would help to oppose osmotic swelling.
F e. water moves up against its concentration gradient

Q. 79. **Facilitated diffusion**
T a. is crrier mediated transport.
T b. is always down hill movements.
F c. is always uphill movement.
F d. does not require energy.
F e. requires energy from ATP.

Q. 80. **Facilitated diffusion**
T a. transports from higher to lower concentration.
T b. is a passive process.
F c. transport lipid soluble substances.
F d. is associated with ATP splitting by ATPase system.
F e. is a form of counter transport.

Q. 81. **Carrier mediated facilitated diffusion**
T a. is used for cellular uptake of blood glucose
T b. transports substances by changing molecular conformation of carrier protein
F c. is a form of active transport
F d. uses cellular ATP.
F e. transports molecules against their concentration gradient

Q. 82. **Concerning the Sodium-Pump**
T a. high energy phosphate bonds can support the operation of the Na^+ pump.
F b. the rate of Na^+ pumping is independent of the internal. Na^+ pump.
F c. the operation of the Na^+ pump is independent of K^+ influx.
F d. the sodium pump is not affected by change in temperature.
F e. the process can be explained in terms of facilitated diffusion.

Q. 83. **By Na^+-K^+ pump**
T a. constant pumping activity is carried out in all cells
T b. cell volume is maintained

F c. Na^+ is actively transported into the cell
F d. K^+ is actively transported out of the cell
F e. equal number of Na^+-K^+ are transported

Q. 84. **Inactivation of the Na^+-K^+ pump will cause**
T a. an increase in the intracellular volume.
F b. an increase in the intracellular potassium concentration.
F c. hyperpolarization of the membrane potential.
F d. an increase in the excitability of nerve cells.
F e. an increase in the flow of sodium out of the cell.

Q. 85. **Transport of Na^+ across the cell membrane occurs by**
T a. diffusion.
T b. primary active transport.
T c. secondary active transport.
F d. osmosis.
F e. filtration.

Q. 86. **Characteristic of voltage gated Na^+ channel include**
T a. both gates remain open for a short period.
T b. it opens with inactivation gate in open state.
T c. it closes with activation gate remaining open.
F d. it opens with inactivation gate with closed state.
F e. it closes with closure of activation gate.

Q. 87. **Voltage gated K^+ channel**
T a. remains closed at resting membrane potential.
T b. has activation gate only.
T c. opens with depolarization.
F d. opens with hyperpolarization.
F e. has activation and inactivation gates.

Q. 88. **Voltage gate Ca^{++} channel**
T a. takes part in action potential.
T b. is permeable to Na^+
F c. is permeable to K^+
F d. is synonamous with Ca^+ pump.
F e. is a fast channel.

Q. 89. **The emetocytosis or reverse pinocytosis requires which ion**
T a. Mg
F b. Na
F c. K
F d. Ca
F e. Cl.

Q. 90. **When solvent is moving in one direction, the solvent tends to drag along some molecules of solute. This is called**
T a. Solvent drug
F b. Filtration
F c. Osmosis
F d. Donnan effect
F e. All of the above.

Q. 91. **All are true about Sodium-Potassium pump**
T a. Needs ATP
T b. Is inactive at 40° C
T c. Is electrogenic
T d. Requires enzymes
F e. Needed for generation of action potential

Q. 92. **Not true regarding Na-K pump is**
F a. Pumps Na against a gradient intracellular
T b. 3 Na exchanged for 2 K
F c. Increases in intracellular Na.
F d. Hypocalcemia inhibits the pump
F e. Non of the above.

Q. 93. **The non-ionic diffusion in body is seen in:**
T a. Both gut and kidney
F b. Gut
F c. Kidneys
F d. All of the above.
F e. None

DNA & RNA

Q. 94. **DNA molecule**
T a. is also found in mitochondria.
T b. contains adenine with its complementary base thymine.
T c. is located in the nucleus.
T d. is double stranded.
F e. has adenine bound with guanine.

Q. 95. **After DNA has replicated the duplicate strands are called**
T a. chromomere.
T b. chromatid.
F c. centromere.
F d. chromosome.
F e. spindle fibers.

Q. 96. **DNA molecules**
T a. contain deoxyribose sugar.
T b. provide genetic code.
T c. are attached with histone.
F d. are distributed in the cytoplasm.
F e. consist of RNA molecules.

Q. 97. **Basic building blocks of DNA are**
T a. purine and pyrimidine bases.
T b. pentose sugar.
T c. phosphoric acid.

F d. amino acids.
F e. proteins.

Q. 98. **Transcription process include**
T a. base pairing of DNA.
T b. breakdown of hydrogen bond.
T c. formation of extron and intron.
F d. base pairing of RNA.
F e. splitting of DNA.

Q. 99. **RNA nucleotide that forms pair with adenine in DNA is**
T a. uracil.
F b. thymine.
F c. guanine.
F d. cytosine.
F e. tyrosine.

Q. 100. **RNA molecule**
T a. is synthesized in the nucleus.
F b. is a complementary copy of the entire DNA.
F c. migrates from nucleus to cell membrane.
F d. is double stranded structure.
F e. contains sugar deoxyribose.

Q. 101. **Role of RNA in the biosynthesis of proteins is**
T a. ending of polypeptide chain.
T b. ending of peptide chain.
T c. initiation of peptide chain.
F d. replication of single stranded RNA molecule.
F e. to control amino acid sequence of many polypeptide chain.

Q. 102. **tRNA molecule**
T a. transfers amino acid to growing polypeptide chain.
T b. is formed from DNA.
F c. is formed from m RNA.
F d. is formed from RNA.
F e. transfers RNA from nucleus to cytoplasm.

Q. 103. **Messenger RNA**
T a. migrates from nucleus to cytoplasm.
F b. carries anticodon.
F c. combines with ribosomal RNA.
F d. is arranged in helical pattern.
F e. is synthesized by translation process.

Q. 104. **RNA polymerase plays role in**
T a. DNA replication.
T b. separation of DNA strand.
T c. RNA formation.
F d. DNA synthesis.
F e. base pairing.

Q. 105. **RNA is**
T a. composed of sugar ribose.
T b. a complementary copy of the entire DNA molecule.
T c. containing hydroxyl ion present in the sugar ribose.
T d. synthesized in the nucleus.
F e. double stranded.

Q. 106. **Activation of RNA nucleotides is done by**
T a. RNA polymerase.
F b. activator protein.
F c. repressor protein.
F d. phosphorylase.
F e. ATPase.

Q. 107. **Nucleotides are**
T a. NAD.
T b. $NADPH^+$
T c. ATP.
F d. RNA.
F e. DNA.

Q. 108. **Gene**
T a. contains information for regulation of cellular activity.
T b. can be lethal for organism.
T c. transfers hereditary characteristics.
T d. can be modified by environment.
T e. can be copied.

Q. 109. ***Base Stacking of DNA is by***
T a. Hyperchromicity
F b. Linear dichromicity
F c. Hypochromicity
F d. Electrophoresis
F e. All of the above.

Action potential

Q. 110. **Action potential consists of**
T a. both depolarization and repolarization.
F b. repolarization and hyperpolarization.
F c. either depolarization or repolarization.
F d. depolarization only.
F e. repolarization only.

Q. 111. **Action potentials**
T a. inhibit further stimulation during the period of depolarization and repolarization.
T b. are produced by threshold stimulus.
T c. are composed of depolarization and repolarization phases.
F d. are associated with a repolarization phase caused by out ward movement of chloride.
F e. are produced by sub-threshold stimuli.

Q. 112. **Equilibrium potential of K^+ is**
- T a. -95 mv.
- F b. -90 mv.
- F c. -80 mv.
- F d. -85 mv.
- F e. -70 mv.

Q. 113. **Equilibrium potential of Cl^- is**
- T a. -70 mv.
- F b. -110 mv.
- F c. -80 mv.
- F d. -90 mv.
- F e. -100 mv.

Q. 114. **Equilibrium potential of Na^+ is**
- T a. +60 mv.
- F b. -60 mv.
- F c. -90 mv.
- F d. -70 mv.
- F e. 0 mv.

Q. 115. **Resting membrane potential is created due to**
- T a. exit of K^+ from the cell.
- T b. Na^+-K^+ pump.
- T c. Na^+ entry into the cell.
- T d. entry of K^+ into the cell.
- T e. exit of Na^+ from the cell.

Q. 116. **The resting membrane potential depends on the concentration gradient of**
- T a. sodium.
- T b. potassium.
- F c. calcium.
- F d. chloride.
- F e. bicarbonate.

Q. 117. **Resting membrane potential of a cell**
- T a. is close to equilibrium potential of K^+
- T b. is contributed by Na^+-K^+ pump.
- F c. indicates its excitability.
- F d. is calculated by Gold man equation.
- F e. is calculated by Nernst equation.

Q. 118. **Resting membrane potential of a spinal motor-neuron is**
- T a. -70 mv.
- F b. -80 mv.
- F c. -90 mv.
- F d. +40 mv.
- F e. -100 mv.

Q. 119. **Resting membrane potential of cardiac muscle cell is**
- T a. -85 mv.
- F b. +70 mv.
- F c. -100 mv.
- F d. -70 mv.
- F e. -100 mv.

Q. 120. **Repolarization phase**
- T a. brings an end to excitation.
- F b. raises the membrane potential level.
- F c. is caused by K^+ leak channel.
- F d. precedes depolarization.
- F e. is associated with opening of sodium& calcium channel.

Q. 121. **Rhythmic discharge of action potential is observed in**
- T a. smooth muscle in the gall bladder.
- T b. cardiac muscle.
- T c. neurons in the respiratory center.
- T d. smooth muscle of GI tract.
- F e. neurons in the vasomotor center.

Q. 122. **Saltatory conduction of nerve impulse**
- T a. is a rapid process.
- T b. is present in myelinated nerve fiber.
- F c. is a slow process.
- F d. means conduction from axon to cell body.
- F e. is present in unmyelinated nerve fiber.

Q. 123. **Propagation of action potential is responsible for**
- T a. glandular secretion.
- T b. nerve impulse.
- T c. cardiac impulse.
- T d. muscle contraction.
- F e. muscle relaxation.

Q. 124. **Threshold for action potential means**
- T a. voltage at which muscle contraction begins.
- T b. minimum depolarization of membrane requiring opening of voltage gated channels.
- F c. voltage at which repolarization begins.
- F d. slow depolarization of the membrane.
- F e. voltage that closes inactivation gate.

Q. 125. **Rhythmicity**
- T a. may be induced by low threshold leve for stimulation.
- T b. requires high membrane permeability to Na^+
- T c. requires high membrane permiability to Ca^{++}
- T d. means repetitive action potential.
- T e. means regular interval between two action potentials.

Q. 126. **Plateau in action potential**

T a. is caused by activation of slow Na^+-Ca^{++} channel.
T b. means sustained depolarization.
T c. is caused by inactivation of fast Na^+ channel.
F d. is caused by inactivation of K^+ channel.
F e. means sustained repolarization.

Q. 127. **Action potentials are produced by**
T a. Na^+ influx
F b. Na^+-K^+influx
F c. K^+ influx
F d. K^+ efflux
F d. Ca^+ efflux

Q. 128. **Resting nerve membrance is more permeable to K than to Na**
T a. 50-100 times
F b. 1-5 times
F c. 20-50 times
F d. 200-500 times
F e. 170-180 times.

Q. 129. **The ionic channels in excitable membrane are lined by**
T a. Proteins
F b. Cephalins
F c. Lipids
F d. Carbohydrates
F e. Fat.

Q. 130. **What provides most of the energy that is used to maintain a normal resting membrane potential of about 70 millivolts inside the neuronal cell?**
T a. The sodium pu mp
F b. The potassium pump
F c. The chloride pump
F d. The calcium pump
F e. Diffusion of chloride ions

Q. 131. **Chemical gradient across cell membrane is maintained chiefly by**
T a. K^+
F b. Na^+
F c. Ca^{++}
F d. Cl^-
F e. Mg^{++}.

Q. 132. **Most diffusible ion in excitable tissue is**
T a. Cl^-
F b. Na^+
F c. K^+
F d. PO_4^-
F e. Mg^{++}.

Q. 133. **The physiologically important anion other than chloride is**
T a. Bicarbonate
F b. Nitrate
F c. Phosphate
F d. Sulphate
F e. Lactate.

Q. 134. **Resting membrane potential is close to the Isoelectrical potential of**
T a. CV
F b. Na^+
F c. Mg^{++}
F d. K^+
F e. Cl^-.

Q. 135. **Resting membrane potential on nerve is determined by concentration of**
T a. Potassium
F b. Calcium
F c. Chloride
F d. Magnesium
F e. Sodium.

Q. 136. **Repolarization in isolated muscle piece fibre proceeds from**
T a. Endocardium to epicardium
F b. Epicardium to endocardium
F c. Left to right
F d. Right to left
F d. Base to apex.

Q. 137. **In excitable cells, repolarization is closely associated with, one of the following events**
T a. K efflux
F b. Na efflux
F c. Na influx
F d. K influx
F e. Cl efflux

Q. 138. **End plate potential follows which law**
T a. Depolarisation
F b. All or none law
F c. Hyperpolarisation
F d. Propagation
F e. contraction.

Q. 139. **The end plate potential is characterised by**
T a. Depolarisation
F b. Propagation
F c. All or non law
F d. Hyperpolarisation
F e. contraction.

Q. 140. **Initiation of impulse starts in**
- T d. Dendritic tree
- F a. Axon
- F b. Axon hillock + initial segment
- F c. Cell body
- T d. soma.

Muscle

Q. 141. **Resting length of muscle fibre**
- T a. is 2 mecrometer.
- T b. means unstreteched length before contraction begins.
- F c. means length of sarcomere at the end of contraction
- F d. means length of stretched muscle fiber before contraction.
- F e. is 4 micrometer.

Q. 142. **During isotonic contraction of a skeletal muscle there is shortening of**
- T a. Sarcomere.
- F b. I band.
- F c. M line.
- F d. A band.
- F e. H band.

Q. 143. **Isometric contraction**
- T a. means no change in the length of muscle fiber during contraction.
- T b. is an energy consuming process.
- F c. means change in tension of muscle fiber.
- F d. means change in the lenght of muscle fiber.
- F e. is associated with work done.

Q. 144. **Maximum efficiency of muscle contraction can be achieved by**
- T a. when velocity of contraction is 30% of the maximum velocity.
- T b. moderate velocity of contraction.
- F c. rapid rate of contraction.
- F d. maximum velocity of contraction.
- F e. slow rate of muscle contraction.

Q. 145. **Cross bridges**
- T a. contain ATPase.
- T b. split ATP before their attachment with actin.
- T c. form power stroke.
- T d. are composed of myosin.
- F e. bind to AtP after their detachment from ADP.

Q. 146. **Excitation of a muscle fiber most directly causes**
- T a. release of Ca^{++} from the sarcoplasmic reticulum.
- F b. splitting of ATP.
- F c. pulling of actin.
- F d. movement of tropomyosin.
- F e. attachment of cross bridges to actin.

Q. 147. **The energy of muscle contraction is most directly obtained from**
- T a. ATP.
- F b. anaerobic respiration.
- F c. myoglobin.
- F d. creatinine phosphate.
- F e. aerobic respiration.

Q. 148. **Relationship of velocity of contraction to load applied is**
- T a. inversely proportional.
- F b. directly proportional.
- F c. negative.
- F d. neutral.
- F e. positive.

Q. 149. **The major cation directly involved in the isotonic contraction of skeletal muscle is**
- T b. Ca^{++}
- F b. Mg^{++}
- F c. H^{+}
- F d. Na^{+}
- F e. K^{+}.

Q. 150. **Ionized calcium is**
- T a. required for neuromuscular transmission.
- T b. present in sarcoplasmic reticulum.
- T c. required for coagulation of blood.
- T d. needed for contraction of muscle.
- F e. required for relaxation of muscle.

Q. 151. **Most of the ATP in red muscle is produced in**
- T a. mitochondria.
- F b. golgi apparatus.
- F c. myofilaments.
- F d. cytosol.
- F e. nucleus.

Q. 152. **The Calcium pump of striated muscle pump Ca^{++} into**
- T a. mitochondria.
- T b. sarcoplasmic reticulum.
- F c. sarcoplasm.
- F d. sarcolemma.
- F e. nucleus.

Q. 153. **A band contains**
- T a. both actin and myosin.
- F b. troponin.
- F c. z disc.
- F d. actin only.

F e. myosin only.

Q. 154. **Actin filaments**
T a. cause clot retraction.
T b. form an elastic support for cell membrane.
T c. are contactile element in platelet.
F d. are present in WBC.
F e. are present in cilia.

Q. 155. **Actin filaments are present in**
T a. in platelets.
T b. in smooth muscle cell.
F c. in fibroblast.
F d. all cell membrane.
F e. in endothelial cell.

Q. 156. **Troponin is composed of**
T a. TN-1
T b. TN-T
T c. TN-C
F d. TN-D
F e. TN-2

Q. 157. **Steps in relaxation of skeletal muscle include**
T a. cessation of interaction between actin and myosin.
T b. Ca^{++} is pumped back into sarcoplasmic reticulum.
F c. binding of acetylcholine to nicotinic receptors.
F d. discharge of motor neuron.
F e. inward spread of depolarization along T tubules.

Q. 158. **Agents causing smooth muscle contraction is**
T a. epinephrine and norepinephrine.
T b. angiotensin
F c. glycine.
F d. nitric oxide.
F e. acetylcholine.

Q. 159. **Smooth muscle possess**
T a. contractility.
T b. syncytial properties.
F c. all or none law.
F d. excitability.
F e. stair case phenomenon.

Q. 160. **Unitary smooth muscle is synonymous with**
T a. visceral smooth muscle.
T b. syncytial smooth muscle.
F c. piloerector smooth muscle.
F d. vascular smooth muscle.
F e. bronchial smooth muscle

Q. 161. **When smoth muscle is stretched within physiological limits**
T a. the membrane dopolarizes.
F b. the muscle relaxes.
F c. syncytial conduction is blocked.
F d. action potentials are not elicited.
F e. the tension that develops is due to elastic elements only.

Q. 162. **The average number of muscle fibres attached to one golgi tendon organ are**
T a. 10-15
F b. 1-3
F c. 5-10
F d. 15-75
T e. 8-10

Q. 163. **The band which disappears on muscle contraction is**
T a. H
F b. I
F c. A
F d. Z
F e. M.

Q. 164. **The band which appears on muscular contraction is**
T a. I
F b. A
F c. H
F d. M or CM
F e. A & H

Q. 165. **In severe exercise muscle spasm occurs due to**
T a. Accumulation of K^+
F b. Accumulation of acetylcholine
F c. Accumulation of ca^{++}
F d. Depletion of sodium
F e. Depletion of ATP.

Q. 166. **High twitch muscle fibres in comparison to low twitch muscle fibres are having more**
T a. Mitochondria
F b. C-AMP
F c. Cytoplasm
F d. Enzymes
F e. ER.

Q. 167. **Calmodulin activates**
T a. Muscle phosphorylase
F b. Protein kinase C
F 0. 2,3 DPG
F d. Glucokinase
F e. Depletion of ATP.

Q. 168. **Thrombosthenin is**
T a. Contractile protein
F b. Coagulation factor
F c. A thrombosis promoting protein
F d. A protein regulation platelet producting

F e. All of the above.

Q. 169. **Increased blood flow in muscle during exercise is not because of**

T a. High lactate
T b. High bicarbonate
F c. Low pH
F d. High CO_2
F e. Low PO_2

Q. 170. **A sprinter utilises in the first 3 to 4 minutes of a race**

T a. Muscle glycogen
F b. Creatinine phosphate
F c. Blood glucose
F d. None of the above
F e. All of the above

Q. 171. **In keletal muscle contraction requires**

T a. Depends on action potential
T b. Recruitment of more number of fibres produces more contraction
T c. Local tension
F d. Increase in the strength of action potential increase contraction.
F e. All of the above

Q. 172. **A unique characteristic of smooth muscle is that**

T a. It can sustain a contraction for prologed periods
F b. Calcium is not required for contraction
F c. Repetitive contractions are not possible
F d. Myosin filaments are not required
F e. ATP is required for contraction

Q. 173. **Curare in therapeutic doses**

T a. Decreases the amplitude of skeletal muscle potential
F b. Prevents propagation of action potential in skeletal muscle
F c. Enhances the action of choline esterase
F d. Enhances the action of catecholamines
F e. All of the above

Q. 174. **Muscles can withstand complete arterial occlusion for**

T a. 1 hour
F b. 1/2 hour
F c. 4-6 hours
F d. 8 hours
F e. 4 hours

Q. 175. **Smooth muscle has the following characteristic**

T a. Chronaxie is longer
F b. Threshold is higher
F c. RMP is greater
F d. Action potential is greater
F e. None of the above.

2
Vitamin

Introduction

Definition : Vitamins are a group of organic nutrients required in small quantities for a variety of biochemical functions and which, *generally*, cannot be synthesized by the body and must therefore be supplied in the diet. *or*

(Ref. Harper's illustrated Biochemistry- 26th Edition, P-481)

Vitamin means vital amine. Vitamin may be defined as a potent organic compounds which is found in food in variable and minute quantity and must be supplied to the animal organisms from external sources, so that specific physiological functions, vital to life, may go on normally. *or*

Vitamins may be defined as organic compounds, other than any of the amino acids, fatty acids or carbohydrates, that are neccssary in small amounts in the diet of higher animals for normal growth, maintenance of health, and reproduction.

(Ref. Bogert's Nutrition and Physical Fitness)

Antivitamins

The group of substances which are present in food and have antagonistic action to the vitamins. They are collectively known as antivitamins.

Example :

1. Dicoumarol are antagonistic to Vit-k.
2. Pyrithiamine, Oxy-thiamine to thiamine (Vit B) etc.

Provitamins

These are the precursor substances which can be converted into vitamin but do not possesses any vitamin activity ie, alpha and beta carotenes are the provitamin of vit-A.

Hypervitaminosis

Occationally, high therapeutic dose of certain vitamins when used for protracted period, tend to toxic symptom known as hypervitaminosis.

Water soluble vitamin rarely produce toxic symptom as their is a renal threshold for them; but fat soluble vitamins are more prone to toxic symptoms.

Classification of vitamin

Depending upon their solubility in water, fats and oils as well as fat solvents vitamins are divided into 2 groups :

A. ***Fat soluble vitamins*** *:* Those present in fats and soluble in fat solvents.

Example :

1. Vitamin A *(retinol, beta-carotenes)*
2. Vitamin D *(cholecalciferol/calciferol/1,25-dihydroxy cholecalciferol)*
3. Vitamin E *(tocopherols, tocotrienols)*
4. Vitamin K *(phylloquinone, menaquinones).*

B. ***Water soluble vitamins*** *:* These are water soluble and includes vitamin B-complexes and vitamin C. It does not stored in the body more than 48-72 hours except B_{12}.

i. *Non-B-complex* :
   a. Vitamin C (ascorbic acid)

ii. *B-complex* :
   a. *Energy releasing :*
      1. Vitamin B_1 *(thiamine)*
      2. Vitamin B_2 *(riboflavin)*
      3. Vitamin $_3$ *(niacin, nicotinic acid, nicotinamide)*
      4. Biotin
      5. Pantothenic acid
   b. *Hematopoietic :*
      1. Folic acid
      2. Vitamin B_{12} *(cyanocobalamine)*
   c. *Other :*
      1. Vitamin B_6 (pyridoxin)
      2. Pyridoxal
      3. Pyridoxamine.

(Ref. Lippincott's Illustrated Reviews- Biochemistry, p-319; Harper's illustrated Biochemistry- 26th Edition, P-482)

Amounts of daily required vitamins :

Vitamin A	5000 IU
Vitamin D	400 IU
Vitamin E	15 IU
Vitamin K	70 µg
Thiamine (B_1)	1.5 mg
Riboflavin (B_2)	1.8 mg
Pantothenic acid (B_3}	Unknown
Niacin	20 mg
Folic acid	0.4 mg
Pyridoxine (B_6)	2 mg
Vitamin B_{12}	3 µg
Vitamin C or ascorbic acid	45 mg.

(Ref. Guyton 11th Edition; Page 875)

Causes of vitamin deficiency

1. Defective intake of vitamins or their precursors in food or as supplements. e.g Malnutrition, Unplanned diet etc.
2. Defect in absorption e.g Diarrhoea, Dysentry, Gastro-enteritis, Coeliac desease, sprue etc.
3. Defect in utilization e.g Wrong way of cooking.
4. Lack of knowledge about health.

Table 2-1. **Vitamins essential or probably essential to human nutrition. (Choline is not listed because it is synthesized in the body in adequate amounts except in special circumstances.**

Vitamin	*Action*	*Deficiency Symptoms*	*Source*
A (A_1, A_2)	Constituents of visual pigments; necessary for fetal development and for cell development throughout life	Night blindness, dry skin.	Yellow vegetables and fruit.
Thiamine (Vitamin B_1)	Cofactor in decarboxylations	Beriberi, neuritis	Liver, unrefined cereal grains.
Riboflavin (vitamin B_2)	Constituent of flavoproteins	Glossitis, cheilosis	Liver, milk
Niacin	Constituent of NAD^+ and $NADP^+$	Pellagra	Yeast, lean meat, liver.
Pyridoxine (Vitamin B_6)	Forms prosthetic group of certain decarboxylases and transaminases. Converted in body into pyridoxal phosphate & pyridoxamine phosphate.	Convulsions, hyperirritability	Yeast, wheat, corn, liver.
Pantothenic acid	Constituent of CoA	Dermatitis, enteritis, alopecia, adrenal insufficiencey.	Eggs, liver, yeast.
Biotin	Catalyzes CO_2 "fixation" (in fatty acid synthesis, etc)	Dermatitis, enteritis	Egg yolk, liver, tomatoes.
Folates (folic acid) & related compounds	Coenzymes for "1-carbon" transfer; involved in methylating reactions	Sprue, anaemia, neural tube defects in children born to folate-deficient women.	Leafy green vegetables.
Cyanocobalamin (B_{12})	Coenzyme in amino acid metabolism. Stimulates erythropoiesis.	Pernicious anemia	Liver, meat, eggs, milk.
Vit-C	Maintains prosthetic metal ions in their reduced form; scavenges free radicles	Scurvy	Citrus fruits, leafy green vegetables.
Vit-D	Increase intestinal absorption of calcium and phosphate..	Rickets	Fish, liver.
Vit-E	Antioxidants ; cofactors in electron transport in cytochrome chain?	Ataxia and other symptoms and signs of spinocerebellar dysfunction	Milk, eggs, meat, leafy vegetables.
Vit-K	Catalyze gama carboxylation of glutamic acid residues on various proteins concerned with blood clotting.	Hemorrhagic phenomena	Leafy green vegetables.

Ref. Ganong 22th Edition, Page 313, 314, 315)

Characteristics of vitamins

The general characteristics of vitamins are-

1. *Distribution :* The vitamins are widely distributed in nature both in animal and plant kingdoms.
2. *Source :* All vitamins are manufactured in plants; only a few are manufactured in animals.
3. *Daily requirement :* Vitamins can perform their work in very low concentration. Hence, the total daily requirement is usually very small.
4. *Store :* Vitamins can be stored in the body to some extent.
5. *Fate :* Vitamins are partly destroyed & partly excreted.
6. Vitamins are not destroyed by digestive process.
7. Some of the vitamins are fat soluble and others are water soluble.

Table 2-2. **Food and Nutrition Board, National Academy of Sciences- National Research Council recommended dietary allowances, revised 1989.**[12]

Fat-Soluble Vitamins :

Category	*Age (years) or Condition*	*Weight*[3]		*Height*[3]		*Protein* (g)	*Vitamin A* (µg of RE)4	*Vitamin D* (µg)5	*Vitamin E* (mg of α–TE)6	*Vitamin K* (µg)
		Kg	lb	Cm	Inch					
Infants	0.0-0.5	6	13	60	24	13	375	7.5	3	5
	0.5-1.0	9	20	71	28	14	375	10	4	10
Children	1-3	13	29	90	35	16	400	10	6	15
	4-6	20	44	112	44	24	500	10	7	20
	7-10	28	62	132	52	28	700	10	7	30
Males	11-14	45	99	157	62	45	1000	10	10	45
	15-18	66	145	176	69	59	1000	10	10	65
	19-24	72	160	177	70	58	1000	10	10	70
	25-50	79	174	176	70	63	1000	5	10	80
	51+	77	170	173	68	63	1000	5	10	80
Females	11-14	46	101	157	62	46	800	10	8	45
	15-18	55	120	163	64	44-	800	10	8	55
	19-24	58	128	164	65	46	800	10	8	60
	25-50	63	138	163	64	50	800	5	8	65
	51+	65	143	160	63	50	800	5	8	65
Pregnant						60	800	10	10	65
Lactating	1st 6 months					65	1300	10	12	65
	2nd 6months					62	1200	10	11	65

[1] Modified,and reproduced, with permission, from Recommended Dietary Allowances, 10th ed, National Academy Press, 1989. Copyright © 1989 by the National Academy of sciences. Couttesy of the National Academy Press, Washington, D.C.

[2] The allowances, expressed as average daily intakes over time, are intended to provide for individual variations among most normal persons as they live in the United States under usual environmental stresses. Diets should be based on a variety of common foods to provide other nutrients for which human requirements have been less well defined.

[3] Weights and heights of Reference Adults are actual medians for the U.S. population of the designated age. The median weights and heights of those under 19 years of age are not necessary the ideal values.

[4] Retinol equivalents. 1 retinol equivalent = 1 µg of retinol or 6 µg of β-carotene.

[5] As cholecalciferol. 10 µg of cholecalciferol = 400 IU of vitamin D.

[6] α-Tocopherol equivalents. 1 mg of *d*-α tocopherol = 1 α-TE.

(Ref. Ganong 22th Edition; Page-312)

Vitamin A

Synonym : Retinol

Structure :

Vitamin A is often used as a collective term for several related biologically active molecules. The term ***retinoids*** includes both natural and synthetic forms of vitamin A that may or may not show vitamin A activity.

a. *Retinol* : A primary alcohol containing a beta-ionone ring with an unsaturated side chain. Retinol is found in animal tissues as a retinyl ester with long-chain fatty acids.

b. *Retinal* : The aIdehyde derived from the oxidation of retinol. Retinal and retinol can readily be interconverted.

c. *Retinoic acid* : The acid derived from the oxidation of retinal. Retinoic acid cannot be reduced in the body and therefore cannot give rise to either retinal or retinol.

d. *Beta carotene* : Plant foods contain beta-carotene, which can be oxidatively cleaved in the intestine to yield two molecules of retinal. In human the conversion is inefficient, and vitamin A activity of beta-carotene is only about one sixth that of retinol.

(Ref. Lippincott's Illustrated Reviews- Biochemistry, p-331)

Table 2-3. **Food and Nutrition Board, National Academy of Sciences- National Research Council recommended dietary allowances, revised 1989.**[12]

Water-Soluble Vitamins :

Category	*Age (years) or Condition*	*Weight*[3] Kg	lb	*Height*[3] Cm	Inch	*Vitamin* C (mg)	*Thiamin* (mg)	*Riboflvin* (mg)	*Niacin* (mg NE)7	*Vitamin* B6 (mg)	*Folate* (µg)	*Vitamin* B12(µg)
Infants	0.0-0.5	6	13	60	24	30	0.3	0.4	5	0.3	25	0.3
	0.5-1.0	9	20	71	28	35	0.4	0.5	6	0.6	35	0.5
Children	1-3	13	29	90	35	40	0.7	0.8	9	1.0	50	0.7
	4-6	20	44	112	44	45	0.9	1.1	12	1.1	75	1.0
	7-10	28	62	132	52	45	1.0	1.2	13	1.4	100	1.4
Males	11-14	45	99	157	62	50	1.3	1.5	17	1.7	150	2.0
	15-18	66	145	176	69	60	1.5	1.8	20	2.0	200	2.0
	19-24	72	160	177	70	60	1.5	1.7	19	2.0	200	2.0
	25-50	79	174	176	70	60	1.5	1.7	19	2.0	200	2.0
	51+	77	170	173	68	60	1.2	1.4	15	2.0	200	2.0
Females	11-14	46	101	157	62	50	1.1	1.3	15	1.4	150	2.0
	15-18	55	120	163	64	60	1.1	1.3	15	1.5	180	2.0
	19-24	58	128	164	65	60	1.1	1.3	15	1.6	180	2.0
	25-50	63	138	163	64	60	1.1	1.3	15	1.6	180	2.0
	51+	65	143	160	63	60	1.0	1.2	13	1.6	180	2.0
Pregnant						70	1.5	1.6	17	2.2	400	2.2
Lactating	1st 6 months					95	1.6	1.8	20	2.1	280	2.6
	2nd 6months					90	1.6	1.7	20	2.1	260	2.6

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2 The allowances, expressed as average daily intakes over time, are intended to provide for individual variations among most normal persons as they live in the United States under usual environmental stresses. Diets should be based on a variety of common foods to provide other nutrients for which human requirements have been less well defined.

3 Weights and heights of Reference Adults are actual medians for the U.S. population of the designated age. The median weights and heights of those under 19 years of age are not necessary the ideal values.

7 1 NE (niacin euivalent) is equal to 1 mg of niacin or 60 mg of dietary tryptophan.

(Ref. Ganong 22th Edition; Page-312)

Sources of vitamin A :

1. *Animal source :* Cod liver oil, halibut liver oil, liver, egg yolk. milk, milk products- butter, cream etc.
2. *Vegetable sources :* Green leafy vegetables, e.g carrots, papyes, yellow mangoes, yellow bananas, spinach.

Daily requirement : 5000 IU (1 IU = 6 Micro gm.)

The RDA for adults is 1000 retinol equivalents (RE) for males and 800 RE for females. One RE = 1 µg of retinol, 6 µg of beta-carotene, or, 12 µg of other carotenoids.

(Ref. Lippincott's Illustrated Reviews- Biochemistry, p-333)

Absorption and transport of vitamin A :

a. *Transport to liver :* Retinol ester present in the diet hydrolyzed in the intestinal mucosa, releasing retinol and free fatty acids. Retinol derived from esters and from the cleavage and reduction of carotenes is reesterified to long-chain fatty acids in the intestinal mucosa and secreted as a component of chylomicrons into the lymphaticsystem. Retinol esters contained in chylomicrons are taken up by, and stored in, the liver.

b. *Release from liver :* When needed, retinol is released from the liver and transported to extrahepatic tissues by the plasma retinol-binding protein (RBP). The retinol-RBP complex attaches to specific receptors on the surface of the cells of peripheral tissues, permitting retinol to enter. Many tissues contain a cellular retinol-binding protein that carries retinol to sites in the nucleus where the vitamin acts in a manner analogous to steroid hormones.

(Ref. Lippincott's Illustrated Reviews- Biochemistry, p-331)

Functions of vitamin A :

a. *Visual cycle* : Vitamin A is a component of the visual pigments of rod and cone cells. Rhodopsin the visual pigment of the rod cells in the retina, consists of 11-cis retinal specifically bound to the protein opsin. When rhodopsin is exposed to light, a series of photochemical isomerizations occurs, resulting in the bleaching of the visual pigment and release of all tras retinal and opsin. Similar reactions are responsible for color vision in the cone cells.

b. *Growth* : Animals deprived of vitamin A initially lose their appetites, possibly because of keratinization of the taste buds. Bone growth is slow and fails to keep pace with gorwth of the nervous system, leading to central nervous system damage.

c. *Reproduction* : Retinol and retinal are essential fcr reproduction, supporting spermatagenesis in the male and preventing fetal resorption in the female. Retinoic acid is inactive in maintaining reproduction and in the visual cycle, but promotes growth and differentiation of epithelial cells; thus, animals given vitamin A only as retinoic acid from birth are blind and sterile.

d. *Maintenance of epithelial cells* : Vitamin A is essential for normal differentiation of epithelial tissues and mucus secretion.

(Ref. Lippincott's Illustrated Reviews- Biochemistry, p-332)

Distribution of vitamin A :

Liver, kidney, cream, butter, and egg yolk are good sources of preformed vitamin A. Yellow and dark green vegetables and fruits are good dietary sources of the carotenes, which serve as precursors of vitamin A.

(Ref. Lippincott's Illustrated Reviews- Biochemistry, p-331)

Storage in the body : Vitamin A is stored in the liver. It may be sufficient to maintain a person without any intake of Vitamin A for upto ten months.

(Ref. Guyton, Wright's)

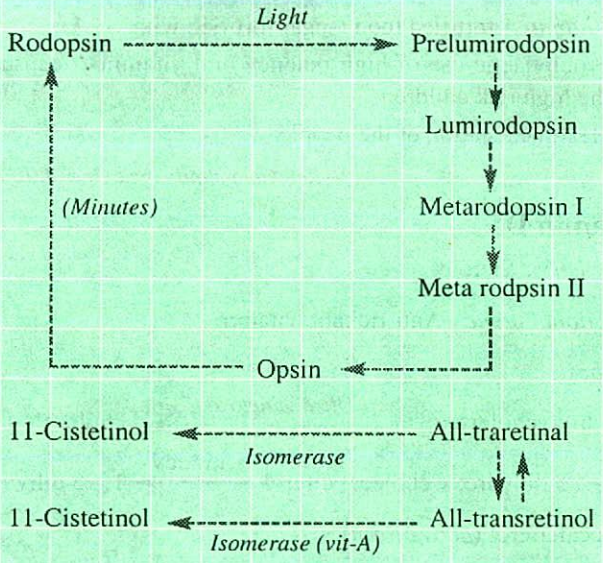
Table 2-1. **Food combinations that provide the recommended daily allowance of total vitamin A activity for an adult.**

	Food	*Amounts*
	Whole milk	1 pt (480 gm)
1.	*Pumpkin pic*	*4 in wedge (150 gm)*
	Vegetable beef soup	1 C
	Margarine or butter	2 t bsp
2.	*Broccoli*	*2/3 C*
	Nectarines	2
	Eggs	2
3.	*Apricots*	*2-4*
	Tomato juice	6 oz

* Each of these food combination furnishes somewhat more than 5000 IU of total vitamin A activity.

(Ref : Bogert's Nutrition & physical Fitness)

Table 2-2. *Diagram of* ***visual cycle***



(Ref. Guyton 11th edition)

Hypervitaminosis A :

Excessive intake of vitamin A produces a toxic syndrome called *hypervitaminosis A.* Amount exceding 7.5 mg of retinol per day should be avoided.

Early signs of chronic hypervitaminosis A are reflected in the skin, which becomes dry and pruritic, the liver, which becomes enlarged and become cirrhotic, and in the nervous system, where a rise in intracranial pressure may mimic the symptoms of a brain tumour.

Pregnant women particularly should not ingest excessive quantities of vitamin A because of its potential for causing congenital malformations in the developing fetus.

(Ref. Lippincott's Illustrated Reviews- Biochemistry, p-331)

Deficiency Sings *(consequences of vitamin A deficiency)* :

In a word vitamin A deficiency produce 'infection'.

1. ***Eye changes*** : Deficiency causes disintrigation of epithelium of cornea and lacrimal gland causes--
   a. *Night blindness* (nyctalopia) : This is the earliest change and is due to les formation of rhodopsin.
   b. *Xeropthalmia* : Cojunctival kertinization.
   c. *Keratomalacia* : Corneal softening and ulceration.
   d. *Bitot's sports* : Triangular, shiny, gray (white plaques) spots on the conjunctiva.
   e. *Corneal scarring* and *blindness.*
2. *Squamous metaplasia* : Squamous metaplasia of columnar mucus-secreting surfaces and transitional epithelium.
   Common sites are : Cornea, conjunctiva, upper respiratory tract, urinary tract, salivary gland, pancrease, sebaceous gland and sweat gland.
3. *Impaired immunity and increased susceptivity* to infections in childhood.

Prevention of Vitamin A deficiency

1. Improvement of diet.
2. *Vitamin A* fortified food (sugar fortified with vit-A)
3. Prophylactic use of high potency oral vitamin-A capsule in the high risk children.
4. Health education of the people.

(Ref. Community medicine; J, E. Park)

Vitamin D

Chemistry : Steroid

Functional name : Anti-ricketic vitamin.

Synthesis :

7-hydroxycholesterol —(*Ultra violet ray*)→ cholecalciferol

liver → 25 dihydroxy cholecal ciferol —(kindey)→ 1, 25 dihydroxy cholecalciferol (*active form*).

Sources :

1. *Animal :* Exposure to sunlight, cod-liver oil, halibut liver oil, liver, egg yolk.
2. Vegetable : Ergot, yeast etc.

Daily requirement : 400 –800 IU.

Functions :

i. It helps in absorption of calcium and phosphorus from the intestine.
ii. It helps in the calcification of new bones.
iii. It leads to proper growth of bone and skeleton.

Deficiency effects :

i. In children : Rickets.
ii. In adult : Osteomalacia : (softening of mature bone)

Toxicosity :

Anorexia, nausea, vomitting, thirst, drawsiness.

Rickets

Features of Rickets : This occurs in children who are not exposed to sunlight and whose diet is deficiet in vit D as well. Typically, this was (it is no longer common in the western world) thus a disease of the poor European children. Poor children of Bangladesh (a sun bathed country), where the custom is to remain bare bodied, are thus free from rickets.

The changes in rickets are as follows :

i. In the bones, the calcium content is low and the bones become therefore soft. Such bones bow when they bear weight, as in femur and tibia.
ii. The process of ossification, in cartilagenous bone is retarded. Normally, the cartilage is first calcified, then removed and then new bones are deposited. In rickets, the calcification of the cartilage is poor, the cartilage cells continue to proliferate and the shaft becomes broad and irregular.

Rarely, the rickets may be due to disease (destruction) of the kidney (renal rickets).

Osteomalacia

If there is lack of vit D in adult life, the condition is called osteomalacia (softness of the bone). It is thus, the counterpart of rickets in adult life. The calcium concentration of the bones is poor, the bones becomes soft and bow under pressure. Deformed pelvic bones (deformed, because of the load of the body weight) may ultimately result in obstetrical problems.

Hypervitaminosis D

Gross intake of vit-D above 10, 000 units usually lead to toxic manifestations characterized by :

i. Nausea, vomitting, diarrhoea with loss of appetite.
ii. Hypercalcimia leads to-
   a. Deposition of Ca in joint soft tissues.
   b. Deposition of Ca in kidney leads to nephro calcinosis, urinary calculi ultimately renal failure and death.
   c. Deposition of Ca in vessels leads to vascular symptoms.

Vitamin E

Synonym : Anti-sterility vitamin.

Chemistry : Tochopherol (alpha, beta, gamma, delta; alpha is most active).

Sources :

1. *Animal :* Eggs, meats, liver, fish, chicken, milk.
2. *Vegetable :* Soya bean, seed oil especially corn, wheat etc.

Daily requirement : 15-20 IU.

Functions :

i. Prevents sterility.
ii. Exerts anti-oxidative effect to protect other vitamins in foods.
iii. Essential for normal function of muscle.
iv. Essential for normal foetal develoment.
v. Necessary for normal reproduction in lower animal.

Deficiency effect :

i. Sterility (loss of reproductive capacity)
ii. Habitual abortion.
iii. Testicular degeneration.
iv. Muscular destrophy.

Viramin K

Synonym : Anti-haemorrhagic factor *(phylloquinone, menaquinones).*

Chemistry : 2- methyl -3 phenyl -1, 4-naphthoquinone.

Sources :

1. *Animal sources :* Are poor, but cheese, egg yolk, liver are good sources. It is also synthesized by intestinal flora.

2. *Vegetable sources :* Green vegetables as spinach, cabbage, peas, cereals, soyabean.

Daily requirement : 70 µg
In haemorrhagic diseases 5 mg orally or in injection form.

Functions :

i. It helps in the formation of prothrombin, factor vii, ix, & x by the liver which takes part in normal coagulation.
ii. It shortens the prothrombin time.
iii. It prevents haemorhage.
iv. It plays an important role in oxidative phosphorylation in the mitochondria.

Blood coagulation effects :

Precursors in liver ---(*Vitamin K*)---> Prothrombin

Calcium → thrombin ---(*Necessary for release of fibrin*)---> Fibrinogen → Fibrin *(Blood Clot)*

Deficiency sign :

i. Hypo-prothrombinemia with resultant prolonged clotting time.
ii. Uncontrolable haemorrhage in new born.
   * Large amount of vitamin K is synthesized by intestinal flora, so dietary deficiency usually does not occur.
   * An important use of vitamin K is as an antidote to the anticoagulant drugs such as dicumerol.

Vitamin B complexes

Vitamin B Complexes :

The members of vitamin-B Complexes are :

i. Thiamin (B_1)
ii. Riboflavin (B_2)
v. Pantothenic acid (B_3)
iii. Niacin
iv. Pyridoxine (B_6)
vi. Lipoic acid
vii. Biotin
viii. Folic acid
ix. Cyanocobalamin (B_{12}).

Thiamin (B_1)

Synonym : Antiberiberi or anti-neurotic vitamin.

Sources :

1. *Vegetables :* Middle coat of cereal grains, peas, pulses, beans, nuts, unpolished rice, is rich in vitamin B_1.
2. *Animal sources :* Generally poor but liver, heart, kidney, egg yolk contains less amount.

Daily requirement : 1.5 mg (average).

	Age	*Allowance mg /day*
Male	11 - 18 yrs	1.4
	19 - 22 yrs	1.5
	23 - 50 yrs	1.4
	51 yrs & over	1.2
Female	11 - 22 yrs	1.1
	23yrs & older	1.0
	Pregnant	+ 0.4
	Lactating	+ 0.5

(Ref : Bogert's Nutrition & physical Fitness)

Functions :

i. Plays an important role in carbohydrate metabolism.
ii. Essential for maintenance of normal appetite and digestion.
iii. Essential for normal function of nervous tissue.

Deficiency sign :

Thiamin (vitamin B_1) deficiency affects predominently the peripheral nervous system, cardiovascular system and the gastro-intestinal tract. The clinical manifestation is known as ***beriberi.***

*The main sympoms of **beriberi** are as follows :*

i. Loss of appetite (anorexia), impaired digestion, severe constipation, gastric atony.
ii. Weakness.
iii. Polyneuritis.
iv. Cardiac failure.

Types of beriberi :

There are three types of beriberi :

i. Dry (*neuritic*)
ii. Wet (*cardiac*)
iii. Cerebral.

(Ref. wright's)

Riboflavin (B_2)

Synonym : Lactoflavin.

Sources :

1. *Animal sources :* Egg yolk, liver, kidney, milk, meat, heart muscles etc.
2. *Vegetable sources :* Green leafy vegetables, peas, beans, cereal grains.

Daily requirement : 1.8 mg (average).

	Age	*Allowance mg/day*
Male	11 - 14 yrs	1.6
	15 - 22 yrs	1.7
	25 - 50 yrs	1.6
	51 yrs & over	1.4

Functions :

i. It acts as co-enzyme in tissue oxidation and respiration.
ii. It helps in protein, fat and carbohydrate metabolism.
iii. Essential for normal growth.

Deficiency sign :

i. Glositis : Inflammation of tongue.
ii. Angular-stomatitis : Cracking at the angle of the mouth.
iii. Cheilosis : Cracking at the line of closure of lips.
iv. Scrotal and vulval dermatitis.
v. Burning sensation of skin, eyes, vascularisation of cornea, mental depression, headache, anorexia, vomitting, forgetfulness.

Niacin

Synonym : Nicotinic acid and pellagra preventing factor.

Sources :

1. *Animal sources :* Milk, milk products, fish, liver, meat, egg, yeast.
2. *Vegetable sources :* Peas, tomato, nuts, maize, vegetables.

Daily roquirement : 15 - 20 mg (average).

	Age	*Allowance mg/day*
Male	11 - 14 yrs	18
	15 - 22 yrs	19
	25 - 50 yrs	18
	51 yrs & over	16
Female	11 - 22 yrs	15
	23 - 50yrs	14
	51 yrs & over	13
	Pregnant	+2
	Lactating	+5

(Ref : Bogert's Nutrition & physical Fitness)

Functions :

i. Prevent pellagra.
ii. Acts as co-enzyme in the form of NAD and NADP.
iii. Essential for the normal functioning of the skin, intestinal tract and nervous system.
v. Essential for growth.

Deficiency sign :

i. Pellagra is characterized by three 'D'- *Dermatitis, Diarrhoea* and *Dementia.*
ii. Glossitis.
iii. Mental depresion.
iv. Stomatitis.

Pellagra : Pellagra means rough skin. At first the skin is red, itchy then becomes swollen and tense and finally desquamation occurs. Here also GI tract disorders occur including irritation and inflammation of mucous membrane of mouth, tongue, gum and other parts of GI tract. Mental changes occur including depression, irritability and delirium.

Pantothenic Acid (B_3)

Pantothenic acid is mainly incorporated in the body into co-enzyme A.

Sources :

1. *Animal sources :* Liver, kidney, egg-yolk, skimmed milk.
2. *Vegetable sources :* Whole grains, cereals, peas, wheat, molasses, sweet potato.

Daily requirement : Unknown, but 5-10 mg is thought to be adequate.

Functions :

It has many metabolic roles in the cells. Example are :

i. Convertion of decarboxylated pyruvic acid into acetyl Co-A prior to its entry to the citric acid cycle.
ii. Degradation of fatty acid molecules into multiple molecules of acetyl Co -A.

Deficiency sign : Deficiency of pantothenic acid in lower animals can cause -

i. Retared growth
ii. Failure of reproduction
iii. Grawing of hair
iv. Dermatitis
v. Fatty liver
vi. Haemorrhagic adrenal cortical necrosis.

In human being no definite deficiency syndrome occurs, because of-

i. The wide occurence of this vitamin in almost all foods.
ii. It probably be synthesized in the body.

Pyridoxin (B_6)

Vitamin B_6 exits in 3 forms- pyridoxine, pyridoxal and pyridoxamine & remains in the cells in the form of pyridoxal phosphate.

Sources :

1. *Animal sources :* Egg yolk, liver, milk, meat, yeast, fish. etc.
2. *Vegetable sources :* Leafy vegetables, corn, wheat, cabbage, legumes.

Daily requirement : 2 mg (average).

	Age	*Allowance mg/day*
Male	11 - 14 yrs	1.8
	15 - 18 yrs	2.0
	19 yrs & over	2.2

Female	11 - 22 yrs	1.3
	23 - 50yrs	1.2
	51 yrs & over	1.2
	Pregnant	+0.3
	Lactating	+0.5
Female	11 - 14 yrs	1.8
	15 yrs & over	2.0
	Pregnant	+0.6
	Lactating	+0.5

(Ref : Bogert's Nutrition & physical Fitness)

Function :

i. It acts as a co-enzyme and involves in trans- amination for the synthesis of aminoacid.
ii. Essential for metabolism of tryptophan.

Deficiency effects :

i. Dermatitis around mouth & eye
ii. Anorexia
iii. Nausea
iv. Vomitting
v. Neuritis
vi. Gastro-intestinal disorders
vii. Convulsion.

Folic Acid

Sources :

1. Animal sources : Liver, kidney, milk, egg.
2. Vegetable sources : Leafy vegetables, beans, nuts and cabbage.

Daily requirement :

Unknown but 50 microgram is thought to be adequate.

Functions :

i. Necessary for maturation of RBC.
ii. Necessary for the synthesis of purines and thymine, which is required for the formation of DNA.

Deficiency effects :

i. Megaloblastic anaemia.
ii. Gastro-intestinal disorders.
iii. Glossitis.

* Severe folate deficiency may cause infertility or even complete sterility.

Recommended allowance for folic acid & vitamin B_{12}.

	Age	*Folic activity mcg /day*	*Vitamin B_{12} activity mcg/day*
Male	11yrs & over	400	3
Female	11 yrs & over	400	3
	Pregant	800	4
	Lactating	500	4

Cyanocobalamin (B_{12})

Synonym : Antipernicious anaemia factor.

Sources : Liver, egg yolk, kidney, milk, cheese & meat.

Daily requirement : 2 micro-gram.

Functions :

i. Essential for maturation and formation of RBC.
ii. Necessary for the synthesis of DNA.

Deficiency effects :

i. Pernicious or magaloblastic anaemia.
ii. Demyelination of the large nerve fibers of the spinal cord specially of the lateral columns.

Storage of vitamin-B complexes in the body : The storage of vitamin-B complexes are relatively slight (48-72 hours). When a person's diet is deficient in vitamin-B compounds, clinical symptoms of the deficiency can some times be recognized within a few days (except for vitamin B12 which can last in the liver for a year or longer).

Vitamin C

Synonym : Ascorbic acid, antiscorbutic.

Sources :

1. Vegetable sources : Fresh citrus fruits, e. g. Amlaki, orange, lemon, guava, pineapple, papay etc. Fresh vegetebles e. g. cabbage, cauliflower, green peppers, spinach, lettuce, tomato etc.
2. Animal sources : Generally poor but milk contains small amount.

Daily requirement : 50-100 mg (average).

	Age	Allowance mg/day
Male	1 - 10 yrs	45
	11 - 14 yrs	50
	15 yrs & over	60
Female	1 - 10 yrs	45
	11 - 14 yrs	50
	15 yrs & over	60
	Pregnant	+20
	Lactating	+40

(Ref : Bogert's Nutrition & physical Fitness)

Functions :

i. It maintain normal intercellular material of cartilage, dentine and bone.
ii. It takes part in wound healing.some metabolic action.
iii. It has some metabolic action.
iv. It prevents scurvy.
v. Large doseses protect against infection.
vi. It is essential for maturation of RBC.

Deficiency effect :

i. Scurvy.
ii. Anaemia.

Scurvy

A deficiency (vit C) disease characterized by haemorrhagic manifestation and abnormal formation of bones and teeth.

Symptoms : Preceded by period of ill health, characterizd by

shallow complexion; loss of energy, pains in leg, limbs, and joints. Anaemia, great weakness, bleeding gums, looseing of teeth, subcutaneous haemorrhages and haemorrhages from mucus membrane etc.

3
Minerals

Minerals

Minerals are inorganic substances required by the organism in very small amounts for its growth and maintenance of its functional activity.

Function of minerals:

i. Minerals are essential constituent of all cells.
ii. Maintenance of osmotic pressure of body fluids.
iii. Needed in the formation of bones and teeth and coagulation of blood.
iv. They regulate the excitability of muscular and nervous system.
v. Play an important role in water metabolism and regulation of blood volume.
vi. Essential in the transport of gases.

Types of minerals :

Minerals are divided into two types :

1. *Principal elements:* These occur in the body in greater concentration (60-80%). These include- sodium, potassium, calcium, magnesium, phosphorus, sulpher and chlorine.
2. *Trace elements:* These occur in the body in lower concentration. These include- arsenic, chromium, cobalt, copper, fluorine, iodine, iron, manganese, molybdenum, nickel, selenium, silicon, vanadium, zinc.

Trace elements believed essential for life.

(Ref. Ganong 21th Edition; Page-313)

Required daily amounts of minerals :

Minerals	*Per day*
Na	3.0 gm
K	1.0 gm
Cl	3.5 gm
Ca	1.2 gm
P	1.2 gm
Fe	18.0 mg
I	150.0 µg
Mg	0.4 gm
Zn	15.0 mg
Co	Unknown
Mn	Unknown
Cu	Unknown

(Ref. Guyton 11th Edition; Page-879)

Sodium

Sources : Table salt, most cereals, milk, fruits vegetables.

Normal Blood level :

Whole blood contains of 160 mg% or 70 mEq/L.

Daily requirement :

3.0 gm (Guyton), Content in adult man - 6.3 gms.

Absorption : Na is absorbed mainly from small intestine & some may from large intestine and stomach. The process is mostly by diffusion.

Excretion : Main channel of excretion is kidney. Only 5% is excreted through urine. Some amount of Na excretes through sweat.

Significance :

i. It is the main base of the body . It is the chief extra cellular cations.
ii. It is one of the important cations responsible for maintaining the internal environment of the body.
iii. It maintains the neuro-muscular conductivity and irritability.
iv. It maintains cardiac rhythmicity and contractility.
v. It froms the alkali reserve of the body.

Potassium

Sources : Cereals, bananas, orange, chicken, beef, liver, vegetables, water etc.

Blood level :

1. Whole blood : 200 mg% or 50 mEq/L
2. Plasma : 20 mg% or 4-5 mEq/L
3. Corpuscles : 440 mg% or 112 mEq/L

Daily requirement : 1 gm

(Ref, Guyton& Hall-11th Edition)

Absorption : It is absorbed from GI Tract along with Na and Cl in the same way as sodium is absorbed.

Excretion :

a. Mostly are excreted through urine. Potassium is not only excreted in the urine but it also added to the urine from distal tubule in exchange for Na^+.
b. Small amount are also excreted through sweat and digestive juice.

Functions :

i. With sodium, it forms the main base of the body. It is the chief intracellular cation.
ii. It is responsible for maintaining the membrane potential of all irritable cells.
iii. It influence the activity of cardiac muscle.
iv. Essential in conduction of nerve impulse.

Hyperkalemia

Definition : Increased level of potasium in serum.

Cause :

i. Addison's disease
ii. Advanced chronic renal failure
iii. Dehydration
iv. Shock
v. Intravenous administration of potassium.

Symptoms :

1. Bradycardia
ii. Peripheral vascular collapse
iii. Cardiac arrest
iv. Mental confusion
v. Weakness of respiratory muscles
vi. Flaccid Paralysis of Limbs.

Hypokalemia

Definition : Decreased level of potassium in serum.

Cause :

i. Chronic wasting disease with malnutrition
ii. Prolonged negetive nitrogen balance
iii. Dirrhoea
iv. Cushing syndrome etc.

Symptoms :

i. Tachycardia
ii. Dilatation of heart.
iii. Muscle weakness
iv. Kidney hypertrophy etc.

Calcium

Sources :

1. Milk (120 mg/100 ml)
2. Milk products (800mg/ 100 ml)
3. Eggs, meats
4. Green vegetable, nuts, potato, rice etc.

Normal plasma calcium level :
10 mg/dl (5 meq/L, 2.5 mmol/L)

(Ganong 22th Edition, page 382)

In plasma calcium remains in three forms :

i. Ionized calcium : 50% (*1.2 mmol/L*), this physiologically active and diffusible.

ii. Protein bound calcium : 41% (*1 mmol/L*), in combination with plasma protein.

iii. Calcium complexed to anions : 9% (*0.2 mmol/L*), is diffusible but is combined with citrate & phosphate.

(Ref. Guyton & Hall-11th Edition, page 978, 979)

or

Distribution (mmol/L) of calcium in normal human plasma :

Total diffusible		1.34
Ionized (Ca^{++})	1.18	
Complexed to HCO3- , citrate etc.	0.16	
Total nondiffusible (protein-bound)		1.16
Bound to albumin	0.92	
Bound to globulin	0.24	
Total plasma calcium		2.50

It is the free, ionized calcium in the body fluids that is a vital second messenger and is necessary for blood coagulation, muscle contraction, and nerve function.

(Ref. Ganong 22th edition, Page-383)

Total body calcium level : 1100 gm
: 27.5 mol

(Ref. Ganong 22th edition, Page-383)

Daily requirement :

1. Average human being : 0.5 gm
2. Adolecent children : 0.7 gm
3. Pregnant and lactating mother : 1.0 gm
4. *Normal* : *1.2 gm.*

(Ref. Guyton& Hall-11th edition)

Absorption : Calcium though presents in nature in both organic and inorganic form, it is absorbed only as inorganic salt in the small intestine mainly in duodenum.

Excretion :

a. Mainly excreted through faeces (0.4 - 0.8 gm).
b. Small amount also excrete through urine (120 - 150 mgm).

Storage : 99% of the body calcium stored in the skeleton.

Significance of calcium :

i. Calcium helps in the formation of bones and teeth.
ii. It helps in clotting of blood and curdling of milk.
iii. It is essential for maintaining neuromuscular excitability.
iv. It helps to maintain cardiac contractility. Excess calcium will make the heart to stop in systole.
v. It is believe to be actively involved in the membrane transport mechanism.

Factors influencing absorption :

1. Calcium-equilibrium of the body : The calcium deficient body absorbs more calcium.
2. Phosphate & Magnesium proportion of diet : High phosphate and low magnesium concentration diet facilitates Ca absorption.
3. P^H of intestinal lumen : Acidic p^H enhance where as alkaline p^H retards absorption.
4. Fatty meal: High fatty diet retards absorption.
5. High protein diet : Helps Ca absorption.

6. Oxalic acid : Retards absorption.
7. Vitamin D : Enhance absorption.

Deficienecy symptom :

i. *Children* : Rickets.
ii. *Adult* : Osteomalacia.

N.B. Features of Rickets descrided in vitamin - D.

Regulation of calcium metabolism

Three hormones are primarily concerned with the regulation of calcium metabolism.

1. *1,25-Dihydroxy-cholecalciferol* : Is a steroid hormone formed from vitamin D by successive hydroxylations in the liver and kidneys.
   Function : Its primary action is to increase calcium absorption from the intestine.
2. *Parathyroid hormone (PTH)* : Is secreted by the parathyroid glands.*Function* : Its main action is to mobilize calcium from bone and increase urinary phosphate excretion.
3. *Calcitonin* : A calcium-lowering hormone that in mammals is secreted primanly by cells in the thyroid gland,.
   Function : Inhibits bone resorption.

Although the role of calcitonin seems to be relatively minor, all three hormones probably operate in concert to maintain the constancy of the Ca^{2+} level in the body fluids.

A fourth hormone, *parathyroid hormone-related protein (PTHrP)*, acts on one of the PTH receptors and is important in skeletal development in utero. There may also be a phosphate-regulating hormone, and glucocorticoids, growth hormone, estrogens and various growth factors also affect calcium metabolism.

Other *electrolytes* and *pH* affect the Ca^{2+} level. Thus for example, *symptoms of tetany* appear at much higher total calcium levels if the patient ***hyperventilates,*** increasing plasma pH. Plasma proteins are more ionized when the pH is high, providing more protein anion to bind with Ca^{2+}.

(Ref. Ganong 22th edition, Page-382)

Calcium metabolism in an adult human

(ingesting 25 mmol; 1000 mg of calcium :

In bones : The calcium in bone is of two types : a *readily exchangeable reservoir* and a much larger pool of *stable calcium* that is only slowly exchangeable.

There are two *independent but interacting homeostatic systems* affecting the calcium in bone.

1. *One is the system* that regulates plasma Ca^{2+} and in the operation of this system, about 500 mmol of Ca^{2+} per day moves into and out of the readily exchangeable pool in the bone.
2. *The other system* is the one concerned with bone remodeling by the constant interplay of bone resorption and deposition, which, in the adult, accounts for 95% of bone formation. However, the Ca^{2+} interchange between plasma and this stable pool of bone calcium is only about 7.5 mmol/L.

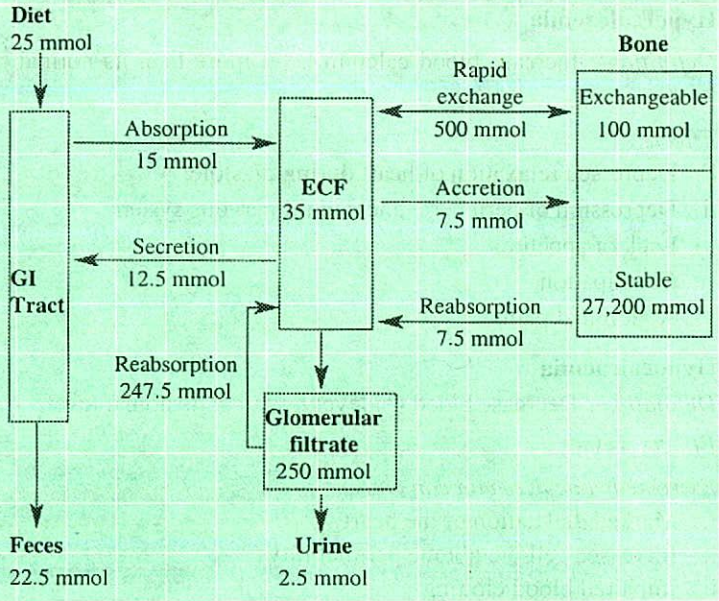


Figure 8-14. *Calcium metabolism in an adult human ingesting 25 mmol (1000 mg) of calcium per day.* (Ref. Ganong 22 th edition; page 383)

In kidneys : A large amount of calcium is filtered in the kidneys. but 98-99% of the filtered calcium is reabsorbed. About 60% of the reabsorption occurs in the *proximal tubules* and the remainder in the *ascending limb of the loop of Henle* and the *distal tubule*. Distal tubular reabsorption is regulated by parathyroid hormone.

In gastrointestinal tract : The absorption of Ca^{2+} from the gastrointestinal tract is actively transported out of the intestine by a system in the brush-border of the epithelial cells that involves a calcium-dependent ATPase, and this process is regulated by 1,25-dihydroxy cholecalciferol. There is also some absorption by passive diffusion. When Ca^{2+} intake is high, 1,25 dihydroxy cholecalciferol levels fall because of the increased plasma Ca^{2+}. Consequently, Ca^{2+} absorption undergoes adaptation; ie, it is high when the calcium intake is low and decreased when the calcium intake is high. Calcium absorption is also decreased by substances that form insoluble salts with Ca^{2+} (eg, phosphates and oxalates) or by alkalis, which favor formation of insoluble calcium soaps. A high-protein diet increases absorption in adults.

(Ref. Ganong 22th edition, Page-382, 383)

Hypocalcemic tetany : A decrease in extracellular Ca^{2+} exerts a net excitatory effect on nerve and muscle cells in vivo. The result is *hypocalcemic tetany*

Characteristics :

1. *Extensive spasms of skeletal muscle*, involving especially the muscles of the extremities and the larynx.
2. *Laryngospasm* becomes so severe that the airway is obstructed and fatal asphyxia is produced.

Ca^{2+}plays an important role in clotting in vivo, however, the level of plasma Ca^{2+} at which fatal tetany occurs is still above the level at which clotting defects would occur.

(Ref. Ganong 22th edition, Page-382)

Hypercalcaemia

Definition : Increase blood calcium level more than its normal level.

Effects :

i. Depressed relaxation of heart during diastole.
ii. Depression of peripheral and central nervous system .
iii. Lack of appetite.
iv. Constipation.
v. Abdominal pain.

Hypocalcaemia

Defination : Decrease blood Ca level less than its nomal level.

Effect : Tetany

Extreme hypocalcaemia can cause :

i. Marked dialatation of the heart
ii. Increased cell membrane permiability
iii. Impaired blood clotting
iv. Changes in cellular enzyme activity.

Tetany

Aetiology :

There is an increased excitability of peripheral nerves due either to a low serum calcium or to alkalosis in which the proportion of the serum calcium in the ionised form is decreased, although the total calcium concentration remains unaltered. Magnesium depletion should also be considered as a possible contributing factor, particularly in malabsorption. The most common cause of hypocalcaemia is a low serum concentration of albumin which does not result in tetany.

Causes of tetany

1. Due to hypocalcaemia
   - Malabsorption
   - Osteomalacia
   - Hypoparathyroidism
   - Acute pancreatitis
   - Chronic renal failure
2. Due to alkalosis
   - Repeated vomiting of gastric juice
   - Excessive intake of oral alkalis
   - Hyperventilation
   - Primary hyperaldosteronism.
   - Coincident acidosis usually prevents tetany.

Clinical features :

i. *In children :* a characteristic triad of carpopedal spasm, stridor and convulsions occurs, though one or more of these may be found independently of the others. The hands in carpal spasm adopt a characteristic position.The metacarpophalangeal joints are flexed, the interphalangeal joints of the fingers and thumb are extended and there is opposition of the thumb (main díaccoucheur). Pedal spasm is much less frequent. Stridor is caused by spasm of the glottis.

ii. *Adult :* Complain of tingling in the hands, feet and around the mouth. Less often there is painful carpopedal spasm while stridor and fits are rare.

Phosphorus

About 80% of the body phosphate is in the bones. Of the rest, the vast majority is organic phosphate and occurs mostly intracellularly. Common examples of such organic phosphates are, nucleotides, ATP, phospholipids, glucose -6-phosphate and so on.

A small amount of phosphate in our blood is inorganic phosphate. In the plasma of blood, both organic and inorganic phosphates are present. A term *acid soluble phosphate* is used by the clinical biochemists, most of the acid soluble phosphate is inorganic phosphate.

The ultimate source of phosphorous of our body is food. Phosphate excretion occurs via urine.

Syndrome due to phosphate deficiency is perhaps unknown. In renal failure serum acid soluble phosphate may become high. Phosphate excretion via kidney is dependent on PTH and vit D.

Sources : Milk, cheese, egg, meat, nuts, peas, vegetables cereals. etc.

Total body phosphorus : 500-800 gm
: 16.1-25.8 mol
85-90% of which is in the skeleton.

Total plasma phosphorus is about : 12 mg/dL

1. *Organic compounds* : two-thirds of the total plasma phosphorus.
2. *Inorganic phosphorus* : Remaining one-third; inorganic phosphorus (Pi) mostly in PO_4^{3-}, PO_4^{2-} and $H_2PO_4^-$.

The amount of phosphorus normally entering bone : is about 3 mg/kg/d (97 µmol/kg/d), with an equal amount leaving via reabsorption.

Aabsorption in GIT : Phosphorus is absorbed in the *duodenum* and *small intestine* by both *active transport* and *passive diffusion*. However, unlike the absorption of Ca^{2+} the absorption of Pi is linearly proportionate to dietary intake. Many stimuli that increase Ca^{2+} absorption, including 1,25-dihydroxycholecalciferol also increase Pi absorption.

Reabsorption in kidneys : The Pi in the plasma is filtered in the glomeruli, and 85-90% of the filtered Pi is reabsorbed. Active transport in the proximal tubule accounts for most of the reabsorption, and this active transport process is powerfully inhibited by parathyroid hormone.

(Ref. Ganong 22th Edition; page 383)

Phosphorus store :

1. In skeleton about : 80 - 85%
2. The rest is distributed through out the body.

Functions :

i. Essential constituent along with calcium for formation of bones and teeth.
ii. Essential in the formation of high energy compounds i.e. ATP.

iii. Essential in the synthesis of RNA, DNA and phospholipids.
iv. Play an important part in all metabolism
v. It comes into the composition of some co-enzyme.

Magnesium

50% of the body Mg occurs in the bone. Of the rest, about 45% occurs within the cell and the remaining 5% in the ECF.
Plasma Mg concentration is between 2 to 4 mg/100ml.

Sources : Vegetables , cereals , egg, milk, soyabean etc.

Daliy requirement : 0.4 gm.

Functions

i. Magnesium ions (Mg^{++}) act as cofactor in many enzyme actions, particularly in those where the action involves splitting of ATP.
ii. Mg^{++} to some extent behaves like the calcium on the neuromuscular system. Mg^{++} deficiency can lead to tetany (but clinically the condition is very rare).

Regulation of magnesium metabolism is poorly known, partly perhaps because of the fact that syndrome due to magnesium deficiency or excess is rare,thus magnesium metabolism has received less attention.

Sulphur

Sources : Nearly whole of the body's sulphur comes from the sulphur containing amino-acids.

a. *Major sources :* Methionine, cysteine, cystine.
b. *Minor sources :*
   1. Glycoproteins
   2. Sulpholipid.

Table 2-1. ***Food and Nutrition Board, National Academy of Sciences- National Research Council recommended dietary allowances, revised 1989.***[12]

Minerals

Category	*Age (years) or Condition*	*Weight*[3]		*Height*[3]		*Calcium* (mg)[8]	*Phosphorus* (mg)	*Magnesium* (mg)	*Iron* (mg)	*Zinc* (mg)	*Iodine* (µg)	*Selenium* (µg)
		Kg	lb	Cm	Inch							
Infants	0.0-0.5	6	13	60	24	400	300	40	6	5	40	10
	0.5-1.0	9	20	71	28	600	500	60	10	5	50	15
Children	1-3	13	29	90	35	800	800	80	10	10	70	20
	4-6	20	44	112	44	800	800	120	10	10	90	20
	7-10	28	62	132	52	800	800	170	10	10	120	30
Males	11-14	45	99	157	62	1200	1200	270	12	15	150	40
	15-18	66	145	176	69	1200	1200	400	12	15	150	50
	19-24	72	160	177	70	1200	1200	350	10	15	150	70
	25-50	79	174	176	70	800	800	350	10	15	150	70
	51+	77	170	173	68	1200	800	350	10	15	150	70
Females	11-14	46	101	157	62	1200	1200	280	15	12	150	45
	15-18	55	120	163	64	1200	1200	300	15	12	150	50
	19-24	58	128	164	65	1200	1200	280	15	12	150	55
	25-50	63	138	163	64	800	800	280	15	12	150	55
	51+	65	143	160	63	1500	800	280	10	12	150	55
Pregnant						1200	1200	320	30	15	175	65
Lactating	1st 6 months					1200	1200	355	15	19	200	75
	2nd 6months					1200	1200	340	15	16	200	75

[1] Modified,and reproduced, with permission, from Recommended Dietary Allowances, 10th ed, National Academy Press, 1989. Copyright © 1989 by the National Academy of sciences. Couttesy of the National Academy Press, Washington, D.C.

[2] The allowances, expressed as average daily intakes over time, are intended to provide for individual variations among most normal persons as they live in the United States under usual environmental stresses. Diets should be based on a variety of common foods to provide other nutrients for which human requirements have been less well defined.

[3] Weights and heights of Reference Adults are actual medians for the U.S. population of the designated age. The median weights and heights of those under 19 years of age are not necessary the ideal values.

[8] Calcium values increased after age 50.

(Ref. Ganong 22th Edition; Page-312)

3. Inorganic sulphate of food
4. A trace of organic food sulphate
5. Thiocyanates etc.

Normal blood sulphur level : 3-5mg % , present in three forms -

i. Inorganic : 0.1 -- 1 mg%
ii. Ehtereal sulphate : 0.1 -- 1 mg%
iii. Neutral sulphur : 2.2 -- 4.5 mg%

Functions :

It is an essential constituent of the protein, keratin which helps in the formation of nail, horns and feathers.

Chlorine

Chlorine is the chief anion of the body. About two thirds of the total anions consists of chloride.

Blood level : 365 gm/100ml.

Significance :

i. The chloride of the HCl of gastric juice comes from chloride of the plasma.
ii. It contributes to the maintenance of electrolyte and water balance.

Iron

Sources :

1. *Vegetable sources :* Raw banana, some green vegetables, wheat, nuts, pulses, etc.
2. Animal sources: Egg, meat, liver, kidney etc.

Normal blood level : 50-60 mg /100 ml

Total amount : About 3-6 gms (average 4 gm).

Daily requirement :

a. Infant : 10 - 15 mg
b. Children :
   1 - 3 years : 15 mg
   4 - 10 years : 10 mg
c. Males :
   11 - 18 yrs : 18 mg
   after 19 yrs : 10 mg
d. Female :
   11 - 50 yrs : 18 mg
   after 51 yrs : 10 mg
e. Adult : 18 mg.

(Ref. Guyton 11th Edition)

Absorption & transport of Iron : Iron is absorbed from the small intestine by active absorptive process or pinocytosis (moderate amount) in ferrous form. It immediately combines with a beta globulin, apotransferrin, to form transferrin, which is then transported in the blood plasma and is distributed throughout the body. Excess iron in the blood is deposited in all cells of the body but specially in the liver cells where it combines mainly with a protein, apoferrin, to form ferrin. This iron stored in ferrin is called storage iron. Smaller quantities of the iron in the storage pool are stored in an extremely insoluble form called hemosiderin.

Excretion : About 0.5-0.4 mg of iron is excreted daily. About 2/3rd of this is in the faeces & sweat; reamaining 1/3rd in the urine.

Storage of iron in body :

a. In haemoglobin : 65%
b. In myoglobin : 5%
c. In liver, spleen, kidney : 15%
d. Only small amount is found in the cytochrome enzymes (e.g. respiratory enzymes).
e. Rest in plasma : 80 - 150 microgram /100ml.

Functions :

i. It is essential for formation of haemoglobin, myoglobin and cytochromes, catalase, peroxidase and certain other enzyme systems.
ii. Necessary for O_2 carries in the blood .
iii. It is an essential constituent of myoglobin and respiratory enzymes.
iv. Iron deficiency leads to hypochromic microcytic anaemia.

Factors affecting absorption :

1. *Acidity of stomach :* Helps absorption by reducing ferric iron present in diet.
2. *Presence of reducing agent :* Like Vit-C, glutathione, S-H group of sulphar containing aminoacids helps absorption of iron.
3. *Excess phosphate :* Hampers absorption.
4. *Iron reserve of the body :* If the reserve is depleted, iron absorption increases.
5. *Form of iron :* Inorganic form is readily absorbed.
6. *Pyridoxine :* Helps iron absorption.

Haemosiderosis : It is a condition of iron deposit in tissues in the form of haemosiderin.

Cause : Malaria, Black water fever & Haemolytic anaemia - causing increased breakdown of R.B.C. and release of excess iron from Hb which then deposit in tissue.

Haemochromatosis : This is a pathological condition, where great increase in haemosiderin (55% iron) deposit takes place in liver, spleen, kidney and other tissue.

Cause : The cause is not definitely known, possibly there occurs excessive absorption of iron from diet, specially rich in iron.

Iodine

Sources : Water (mainly sea water) sea fish, Cod liver oil, iodized salt etc.

Iodine Metabolism : Iodine is a raw material essential for thyroid hormone synthesis. Ingested iodine is converted to iodide and absorbed.

1. *Minimum daily iodine intake* : The minimum daily iodine intake that will maintain normal thyroid function is 150 µg in adults, but in the United States the average dietary intake is approximately 500 µg/d.
2. *Normal plasma I^- level* is about : 0.3 µg/dL.

3. *I^- is distribution :*
   a. I^- is distributed in a 'space' of approximately 25 L (35% of body weight). The principal organs that take up the I^- are the thyroid, which uses it to make thyroid hormones, and the kidneys, which excrete it in the urine.
   b. About 120 µg/d enter the thyroid at normal rates of thyroid hormone synthesis and secretion. The thyroid secretes 80 µg/d as iodine in T_3 and T_4.
   c. 40 micrograms of I^- per day diffuses into the ECF.
   d. The secreted T_3 and T_4 are metabolized in the liver and other tissues, with the release of 60 mg of I^- per day into the ECF.

   The total amount of I^- entering the ECF is thus 500 + 40 + 60, or 600 µg/d; 20% of this I^- enters the thyroid, whereas 80% is excreted in the urine.
5. *Excretion* : Some thyroid hormone derivatives are excreted in the bile, and some of the iodine in them is reabsorbed (enterohepatic circulation), but there is a net loss of I^- in the stool of approximately 20 µg/d.

(Ref. Ganong 22th Edition)

Functions : Iodine is essential for the synthesis of thyroid hormones (thyroxine, tri-iodothyronine).

Deficiency disease :

i. Children : Cretinism.
ii. Adult : Goiter and hypothyrodism, Myxedema.

Fate of Iodine : After absorbtion from the intestine iodides do not remain in blood for a long time because the kidneys have high iodide clearance about 35ml/min. So, 4/5th of ingested iodide are lost in urine within first three days and remaining 1/5th is used for thyroid hormone synthesis.

(Ref. Guyton 11th edition)

Manganese

Sources : Liver, Kidney, blueberries, lettuce, pineapple, spinach etc.

Function :

i. It catalyzes along with copper, the synthesis of haemoglobin.
ii. It activates some enzyme action- phosphatase, carboxylase and peptidase etc.

Flourine

Sources : Water, diet.

Function : It is found in bone and teeth, where it prevent caries.

Cobalt

Sources : Foods of animal origin.

Functions :

It stimulates RBC formation by helping formation of Vit -B_{12}.

Zinc

Sources : Meat, liver, eggs and sea food are good sources. Milk and whole grain products, whole wheat or dye bread, oatmeal are also good sources.

Functions :

i. Zinc is a component of certain enzymes such as carboxy peptidase, carbonic anhydrase, alcohol dehydrogenase etc.
ii Zinc is an integral and essential element of insulin and hence necessary for optimal insulin action.
iii. It is also necessary to maintain normal concentration of vitamin A in the plasma. It is required to mobilize vitamin A from the liver.
iv. Necessary for tissue repair and wound healing.
v. Necessary for taste buds.

Daily requirement :

i. Pre-adolescent children : 6-10 mg/day.
ii. Adolescent children : 13 mg/day.
iii. Adult : 15 mg/day.
iv. During pregnancy & lactation : Additional allowance of 15 mg & 10 mg should be added respectively.

Deficiency sign :

i. Growth failure and sexual infantalism in adolescent.
ii. Loss of taste acuity
iii. Delayed wound healing
iv. Hepatosplenomegaly
v. Delayed closure of the epiphysis of long bones
vi. Anaemia
vii. Necessary for tissue repair and wound healing.

Biochemistry

Solution

Definition : It is a homogeneous mixture of two or more components constituting one phase only.

Solution = Solvent + Solute.

Part of Solution : Solution has two parts -

a. *Solvent :* The substance present in larger amount (more than 50%) in a solution is called solvent.

b. *Solute :* The substance present in lesser amount (less than 50%) in a solution is called solute.

Classification of Solution

A. ***On the basis of their physical appearance :***

i. *Saturated solution :* A saturated solution is one in which there is an equilibrium between the solution and undissolved solute at the temperature of the solution. If there is addition of solute it will remain undissolve.

ii. *Unsaturated solution :* An unsaturated solution is one in which the solvent is capable of dissolving more of the solute at a definite temperature of the solution.

iii. *Supersaturated solution :* A solution containing undissolved solute particles at a definite temperature of the solution. Some solutes, form a saturated solution and others remain undissolved.

B. ***On the basis of their permeability through the cell membrane :***

i. *Colloidal solution :* If the solute particles can not pass through the semipermeable membrane ; then the solution is called colloidal solution e.g. Aggregation of albumin solution, plasma, dextran etc.

ii. *Crystalloid solution :* If the solute paticles can pass through the semipermeable membrane then the solution is called crystalloid solution i.e cane suger solution, normal saline, dextrose saline, cholera saline etc.

C. ***On the basis of their concentration :***

i. *Percent solution :* Percent is used in expression of concentrate has the usual meaning of per hundred.

a. *Percent by weight (wt /wt) :* This indicates the gm of solute per 100 gm of solution i.e 38% HCl by weight.

b. *Percent by volume (wt./V):* This indicates the gms of solute per 100 ml of solution i.e 5% NaCl in water.

c. *Percent by volume (V/V) :* This indicates the milliliters of solute per 100 ml of solution i.e gm of solute/100 ml eg. 5% DA.

ii. *Molar solution :* It is a solution which contain 1 gm molecular weight of solute per liter of solution. Gram molecular weight of HCl = 36.5 gm.

So, molar solution of HCl contain 36.5 gm/ liter.

iii. *Molal solution :* It is a solution which contain 1 gm molecular wt. of solute in 1000 gm of solvent. Molal solution of HCl contains 36.5 gm/kg.

iv. *Normal solution :* It is a solution which contain 1 gm equivalent wt. of solute per liter of solution. Gm. eq. wt. of H_2SO_4 = 49. So, normal solution of H_2SO_4 contain = 49 gm/ liter of solution.

v. *Osmolar solution :* It is a solution which contains one osmole of sloute per liter of solution.

D. ***On the basis of tonicity :*** It is used to describe the effective osmotic pressure of a solution relative to plasma.

i. *Isotonic :* Solution which have the same osmotic pressure as that of plasma. E.g. 0.9% NaCl or 5% glucose soln. is isotonic to plasma.

ii. *Hypertonic :* A solution which has higher osmotic pressure than that of plasma .

iii. *Hypotonic :* A solution which has lower osmotic pressure than that of plasma.

Different forms of solution

1. Liquid (solute) with liquid (solvent) e.g. Bromine water.
2. Solid (solute) with liquid (solvent) e.g Sugar in water.
3. Gas (solute) with liquid (solvent) e.g. Soda water.
4. Gas (solute) with gas (solvent) i.e. Air. It is a mixture of O_2, N_2, CO_2 etc.
5. Solid (solute) with solid (solvent) i.e brass. It is a mixture of Cu & Zn.

Preparation of a solution in the Laboratory

Apparatus required :

i. Analytical balance
ii. Funnel
iii. Volumetric flask with stop cork
iv. Beaker
v. Stirer.

Procedure : At first the required solute is measured by an analytical balance. Then take it in a beaker. Add some solvent to the beaker and mix it thoroughly by a stirer. Then transfer the solution by the help of funnel to the volumetric flask. Repeat the procedure for several times so that almost all the solvent can be transfered to the volumetic flask. Stop the flask by stop cork.

Osmole

It is the amount of solute in gms. which gives rise to an osmotic pressure of 22.4 standard atmosphere, when dissolved in one liter of solution.

One osmole is the number of particles in a gram molecular weight of undissociated solute. So, 180 gm of glucose in solution will be 1 osmol of glucose as the molecules do not dissociate.

If a solute like sodium chloride, two ions dissociate in solution. So 58.5 gm. (1 gm mol) of sodium chloride will be 2 osmole.

$$\text{Osmol} = \frac{\text{Molecular weight of a solute in gm}}{\text{The number of ions or particles which dissociates in solution}}$$

Osmolality : Osmoles per kg of water is called osmolality.

Molarity : Number of moles /L e.g mmol/L.

Normality : Number of equivalent/L e.g meq/L.

Osmolarity

Osmoles per liter of solution is called osmolarity i.e number of osmole/L (mosm/L).

a. *Example* : ***Plasma osmolarity*** = 280 - 300 mosm/L.
   i. Nacl : 92 % (crystaloid)
   ii. Others : 8 % (other crystaloid = 7.5%; colloid = 0.5%).
   (Plasma protein = 0.5% = 1.5 mosm/L
   Colloidal osmotic pressure = 25 mm of H
   Crystalloid osmotic pressure = 298.5 mosmm/L)

b. Relation between osmolality to osmotic pressure :
Osmotic pressure (mm of Hg) = 19.3 x osmolality (mosm/liter).

c. ***Osmolar gap*** :
Osmolar gap = Measured osmolarity - calculated osmolarity
= 0 - 12 mosm/L
Osmolar gap increases in :
1. Gross hyperproteinaemia
2. Gross hyperlipidaemia
3. Unmeasured osmotic solutes in plasma eg. manitol, alcohol etc.

d. *Consequences of osmotic disequilibrium* :
1. *Cellular dehydration* : may leads to cerebral dehydration. Upto 20% cellular dehydration can be tolerated by body itself- for ordinay cell and upto 10% cellular dehydration can be tolerated by brain cell.
2. *Cellular over hydration* : may leads to oedema.

Iso-osmotic

Any two solution having the same osmotic pressure or osmolarity are called iso-osmotic to each other.

Concentration

The concentration of a solution means that the weight of the substance dissolved in unit volume of solution.

Standard Solution

It is that solution whose strength and concentration is known. Standard solution are :

i. Molar solution
ii. Molal solution
iii. Normal solution
iv. Osmolar solution
v. Percent solution.

Molecular weight

Molecular weight of any compound means the atomic weight of the component elements in their proper proportion in that compound.

e.g. molecular weight of NaCl = 23 + 35.5 = 58.5.

Gram molecular weight

Molecular weight expressed in gm is known as gram molecular weight e.g. gram molecular weight of NaCl = 58.5 gm.

Equivalent weight

The equivalent weight of a reactive unit is that weight which combines with or replace one atomic weight of hydrogen (1.008 ; or same reacting value of hydrogen.

Equivalent weight = molecular weight / valency

Gram equivalent weight

1. Equavalent weight expressed in gm is known as gram equavalent weight.
2. *Milli-equivalent* weight : It is one thousandth of the gm-equavalent weight.

Normal Saline

0.9% NaCl solution is called normal saline.

Atomic weight

The atomic weight of an element is a number which express how many times the weight of atom of the element is greater than the weight of one atom of hydrogen.

1. Atomic weight = Weight of 1 atom of element/weight of 1 atom of hydrogen.
2. One gram molecular weight of any substance contains 6.023 x 10^{23} (Avogadro number) particles. Thus 180 gm of glucose, 58.5 gm of Nacl represents 6.023 x10^{23} particles.

Collloids & Crystaloid

Colloid

Definition : Colloid may be defined as a substance in which the solute particles are proportionately larger than solvent and is slowly diffusible and is incapable to pass through a semi-permeable membrane. ***or***

Colloids are the substances which by virtue of their molecular size are slow diffusible rather than soluble in water and are incapable of passing through a semi-permeable membrane.

Example :

1. Proteins (plasma protein)
2. Polysaccharides (starch, gelatin, glycogen)
3. Lipids
4. DNA & RNA etc.

Parts of colloidal solution :

a. *Dispersed phase :* The solute part of the colloidal solution is called dispersed phase. It is discontinuous phase.

b. *Dispersion media :* The solvent part of the colloidal soln. is called dispersion media. It is a continuous phase.

Classification of colloids

According to the physical state of the dispersed phase in relation to dispersion media a colloid may remains in two states

a. *Sol :* Here the colloidal solution remains in liquid state, the dispersed phase is solid and the disperson media is liquid e.g milk.

b. *Gel :* When the colloidal solution remain in solid state, the dispersed phase is liquid and the dispersion media is solid then it is called gel e.g butter.

Types of colloidal solution

Colloidal solution fall into two classes -

a. *Emulsoid or lypophilic* : Here both the dispersed phase and dispersion media are liquid, and the solute has a great affinity for the solvent eg. milk.

b. *Suspensoid or lypophobic* : Here the dispersed phase is solid and the dispersion media is liquid and there is no affinity between solute and solvent eg. antacid syrup.

Some colloid & crystalloid solutions

Colloid	*Crystalloid*
i. Plasma.	i. Normal saline
ii. Dextran etc	ii. Dextrose saline.
	iii. Cholera saline etc.

Process of separation of colloid

Separation of colloids may be done by -

1. Dialysis
2. Isoelectric precipitation.
3. Salting out
4. Electrophoresis
5. Adsorption
6. Ultracentrifugation
7. Ultrafiltration.

Properties of colloids :

A. *General properties* :

1. Variable colour. Example : Gold solution- red, silver solution- grey, sulphate solution- colourless etc.
2. Variable shape : usually spherical.
3. Size : 1 - 200 mμ
4. Low osmotic pressure : Plasme colloidal osmotic pressure = 28 - 32 mm of Hg.
5. Imbibition of water : I gm of albumin (colloid) can hold 17 ml of H_20.
6. By dialysis crystalloid can be separated from colloid.
7. Solution can be converted into sol or gel state.

B. *Optical properties* :

1. *Brownian movement* : The continuous, hapazard, irregular, zigzag movement of colloidal particles is known as Brownian movement. That can be seen under the ultramicroscope.
   a. *Reason of motion* : The pushing effect of solvent molecule.
   b. *Rate of motion* : Depends on the size of colloid molecules. The smaller the molecule, the greater the movement.
2. *Tyndall phenomenon* : When a beam of light is passed through a colloidal solution & is observed from right angle, the colloidal particles become visible due to the dispersion of light by the colloid particles. This is known as Tyndall phenomenon.

C. *Electrical properties* :

1. *Electrophoresis* : Colloidal particles carry electrical charges on surface. When an electric current is passed through the colloidal solution, positively & negatively charged particles move to the opposite poles. This is known as electrophoresis.
   a. *Rate of electrophoresis depends upon* :
      i. Size &
      ii. Amount of charge.
2. *Isoelectric pH* : It is the pH at which the colloids exist in solution as 'Zwitter ion' containing equal number of positive & negative charges on their surface. So the net charee is zero. At pH above the isoelectric pH, they will exist as anion and at pH below their isoelectric pH, they will exist as cation.

D. *Other properties* :

a. *Interfacial tension* : Colloid particles exert great interfacial tension which results in irnbibition of water and adsorption of many substances by them.
b. Donnan membrane equilibrium
c. Sol to jel or jel to sol formation
d. Coagulation & salting out.

Functions of colloids in our body :

1. Some of the biological fluids are colloidal solution e.g. blood, milk, CSF etc.
2. Biological compounds as colloidal particles : protein, lipid, polysaccharides.
3. Blood coagulation : when blood is clotted, it forms a gelly like substance.
4. Fat digestion and absorptjon : bile in the intestine emulcifies fat.
5. Format ion of urine.

Importance of colloids

1. Essential constituents of cell cytoplasm.
2. Exert colloidal osmotic pressure required for the fluid exchange in the capillary.
3. Tissue fluid is imbeded by colloids and in this way a good deal of water remains stored in the body.
4. Colloidal sate is responsible for the so called selective absorption or selective membrane permeabilities of certain ions.

Crystalloid

1. *Definition* : A crystalloid may be defined as a substance which can pass through a semi-permiable membrane & cannot be separated by ultracentrifugation.
   Example : Electrolytes (Na^+, K^+, Ca^{++} etc), minerals, vitamins, glucose, amino acid, fatty acid.

Properties of crystalloids :

1. Size : Less than 1 mμ
2. Solute : Are smaller than the solvent particles
3. Permeability : Can pass through the semi-permeable membrane.
4. Physical form : Crystaltic and can be crystalised from solution.
5. Visibility : Can not be seen under ultramicroscope
6. Dialysability : Dialysable
7. Osmotic pressure : High
8. Optical activity : Don't exhibit
9. Movement : Molecular
10. Conversion : Cannot be converted into sol & gel state.
11. Separation : Can not be separated. by ultrafiltration & ultracentrifugation.

Differentiate colloids from crystalloids

Traits	*Colloid*	*Crystalloid*
1. Size	1-200 mμ	Less than 1 mμ
2. Solute	are larger than the solvent particles	are smaller than the solvent particles
3. Permeability	Cannot pass through the semi-permeable membrane.	Can pass
4. Physical form	Amorphous and has no definite shape solution.	Crystaltic and can be crystalised from
5. Visibility	Colloid particles can be seen under ultramicroscope	Can not be seen.
6. Dialysability	Non dialysable	dialysable
7. Osmotic pressure	Low	High
8. Optical activity	Exhibit	Don't exhibit
9. Movement	Brownian	Molecular
10. Conversion	Solution can be converted into sol & gel state.	Cannot be converted
11. Separation	Can be seperated by ultrafiltration & ultracentrifugation	Can not be separated
12. Example	Plasma protein, lipid, starch, glycogen, DNA & RNA.	Electrolytes, minerals, vitamins, glucose, amino acid, fatty acid.

Differentiate Emulsoid & Suspensoid :

Emulsoid	*Suspensoid*
1. Here both dispersed phase and dispersion liquid.	1. Here dispersed phase is solid & the media are dispersion media is liquid.
2. The solute have a great affinity for the solvent.	2. There is no affinity between solute and solvent.
3. Emulsoid is reversible.	3. Suspensoid is irreversible.
4. It is stable colloidal solution.	4. It is less stable than emulsoid.
5. Well defined under microscope & ultramicroscope	5. Invisible under microscope & ultramicroscope
6. Not easily precipitated by salts.	6. Easily precipitated by salts.
7. Particles surrounded by the shell absorbed water	7. Particles not surrounded by water shell
8. Lower surface tension and much higher viscosity than the solvent.	8. Surface tension and higher viscosity of suspensoids are rearly the same as those of the solvent.

Differnce between sol and gel :

Sol	*Gel*
1. Colloid particles bind loosely with one another.	1. Colloid particles bind firmly with one another.
2. Here dispersion media is continous.	2. Here dispersion media is formed by hydrated colloid particles.

Acid Base Balance

Electrolytes

Electrolytes are the compound which can be dissociated into anion and cation on an electric current being passed. e. g Acid, base.

Non-Electrolytes

The compound which can not be dissociated into anions and cations on an electrical current being passed. e.g Cane sugar soln.

Ions

Ions are the charged particles, which moves towards the positive pole (anode) or negative pole (cathod). They are formed when electrical current being passed through a solution of electrolytes.

a. Ions moves toward the positive pole is called anion.
b. Ions moves toward the negative pole is called cation.

Differnce between ions & electrolyte :

Ions	*Electrolyte*
1. Ions are charged particles.	1. Electrolytes are neutral.
2. Ions does not gives rise to electrolyte.	2. Electrolytes gives up ions when placed in a electric field.
3. Ions moves towards the opposite pole.	3. No such movement occurs.
4. Pathway of ions can be traced by electrophoresis.	4. Electrolytes does not give such electrophoresis.

Particles

Particles may be the molecule or fraction of molecule or aggregation of molecules.

Molecules e.g glucose. Fraction of molecule e.g in NaCl - Na & Cl. Aggregation of molecules e.g albumin.

Hydrophilic

If the dispersed phase of colloidal solution is liquid and the dispersion media is water then it is called hydrophilic. Here the solute has a great affinity for water.

Hydrophobic

If the dispersed phase of colloidal solution is solid and the dispersion media is water then it is called hydrophobic. Here the solute has no affinity for water and repeal each other.

Acid

Definition : Acid is the substance, which produces hydrogen ion (H^+) when dissolved in water e.g HCl, H_2CO_3.

i. It is proton (H^+) donar
ii. A solution is acid because there are more H^+ than OH^-.

Types of Acid :

There are two types of acid

i. *Strong acid* : The acids which can dissociated fully (strongly) when dissolve in water e.g HCl, H_2SO_4 etc. Usually all the inorganic acids are strong acids except H_2CO_3.
ii. *Weak acid* : The acids which can dissociated partially (weakly), when dissolve in water e.g lactic acid, acetic acid, H_2CO_3 etc. Usually all the organic acids are weak acids.

Concentrated acid : Acid in molecular form.

Dilute acid : Acid in ionized form.

Difference between strong and weak acid

Strong acid	*Weak acid*
1. It dissociates quickly and strongly.	1. It dissociates slowly and partially.
2. Here conjugate base is weak.	2. Here conjugate base is strong.
3. It is irreversible in reaction.	3. It is reversible in reaction.
4. Usually these are inorganic acid.	4. Usually these are organic acid.

Properties of acid

1. It produces hydrogen ion in aqueous solution.
2. It produces salt and water with alkali
3. It converts blue litmus into red litmus.
4. It is sour in taste.

Strength of an acid

Strength of an acid is determined by

1. The strength of the conjugate base.
2. The basic strength of the solvent.
3. The dielectric constant of the solvent.

Acidity

The state of being acid or acid content of a fluid is known as acidity.

Types of acidity :

1. *Actual acidity* : This is the concentration of H^+ ion in a solution. It is spoken as pH.
2. *Free acidity* : This is the amount of free acid which is present in the solution, not in combination with other compound.
3. *Combined acidity* : Amount of acid present in combination with organic compound (e.g. proteins) and that present in acid salts.
4. *Total acidity* : Amount of free acid plus that present in combination. Free acid+ combined acid= total acid.
5. *Titrable acidity* : Amount of total ionizable hydrogen both ionized and non-inoized, determined by titration against a base. The concentration of H^+ions in a solution plus those available for ionization although not actually ionized at the time.

Base

Definition : The substance which can receive hydrogen ion (H^+)

is called base e.g OH^-, Cl^-, HCO_3^- etc.

i. It is proton (H^+) acceptor.

ii. A solution is alkaline because there is more hydroxyl ion than H^+.

Types of base :

i. *Strong base :* The base which ionized completely in solution and produces a lot of hydroxyl ion (OH^-) e.g NaOH, KOH etc.

ii. *Weak base :* The base which ionized partially in solution and produces small amount of hydroxyl ion (OH^-) e.g. NH_4OH.

Conjugate base

The electro-negative portion of acid which receives hydrogen ion or proton to form acid is known as conjugate base.

* The conjugate base of strong acid is very weak. So strong acid dissociate very quickly and strongly.
* The conjugate base of the weak acid is strong. So the weak acid dissociate weakly and partially.

Alkali

The substance which can donate OH^- ion in aqueous solution is called alkali.

Example : NaOH $Na^+ + OH^-$. Here NaOH is alkali but hydroxyl ion (OH^-) is base.

Properties of alkali :

1. It produces hydroxyl ion in aqueous solution.
2. It produces salt and water with acid.
3. It convert red litmus into blue.

Difference between acid and alkali

Acid	*Alkali*
1. It produces hydrogen ion in water.	1. It produces hydroxyl ion in water.
2. It produces salt and water with alkali.	2. It produces salt and water with acid.
3. It converts blue litmus into red.	3. It converts red litmus into blue.

Basic : Relating to a base of any kind is called basic.

Basicity : The state of being base or base content of a fluid is known as basicity.

Alkaline : Relating to an alkali, having the reaction of an alkali, called alkaline.

Alkalinity : The state of being alkali is known as alkalinity.

Alkalinuria : The passage of alkaline urine.

Alkalizer : An agent that neutralizes acid, called alkalizer.

pH

pH is the negative logarithm of hydrogen ion concentration to the base 10.

$$pH = -\log (H+)$$
$$= \log (1/H^+)$$

(P indicates the negative logarithm to base 10)

So there is inverse relationship between the pH and hydrogen ion concentration. If hydrogen ion concentration increases, P^H decreases and vice versa.

Normal body pH	:	7.35 - 7.45 (average 7.4)
Clinical safe pH	:	7.3 - 7.5
pH compitable to life	:	6.8 - 7.8
If the pH is above the 7.8	:	Death occurs due to tetany and cardiac arrest.

pH 7 :

$H^+ = 10^{-7}$ mole/L
$= 10^{-7} \times 10^9$
$= 10^2$
$= 100$ nmol/L

pH 6 :

$H^+ = 10^{-6}$ mole/L
$= 10^{-6} \times 10^9$
$= 10^3$
$= 1000$ nmol/L

Significance of pH :

It is the measure of extent of acidity or alkalinity of a solution.

Importance of pH :

1. Maintenance of enzyme activity
2. Maintenance of cellular viability
3. Maintenance of neuromuscular irritability.

Optimum pH

The P^H at which most of the physiological enzymatic reaction occurs is known as optimum pH.

pH Scale

Sorensen introduced the simple pH scale. The degree of acidity or alkalinity can be measured on a scale of P^H unit.

pH Scale	:	0 - 14
pH 7	:	neutral.
pH less than 7	:	acidic.
pH more than 7	:	alkaline.

pH 7 : $H^+ = 10^{-7}$ mole/L $= 10^{-7} \times 10^9 = 10^2 = 100$ nmol/L

pH 6 : $H^+ = 10^{-6}$ mole/L $= 10^{-6} \times 10^9 = 10^3 = 1000$ nmol/L

Expresion of acidity :

pH	*H^+ concentration (nmole/L)*
6.8	160
7.3	50
7.35	45
7.4	40
7.45	35
7.5	30
7.8	16

Salient features of pH scale :

1. For unit change of pH, (H^+) will change inverssly 10 times and (OH^-) will chane direcly 10 times.
2. At neutrality (H^+) is equal to 10^{-7} moles/L and neutral pH will be 7.
3. At 25°C Kw = 10-14 and so pH + p OH = 14
4. Acidity means (H^+) more than (OH^-) and alkalinity means (OH^-) more than (H^+).
5 Even an extreme acidic solution contain some amount of OH^- ions and even an extreme alkaline solution contain some amount of H^+ ions.

Q. ***What do you mean by P^H of a solution = 7?***

Ans.

i. It is the solution contains 10^{-7} gmeq./L of hydrogen ion (H^+)
ii. It is the pH of water.
iii. It means the solution is neutral.

Calculation of P^H of a solution :

For the calculation of pH, (H^+) ion concentration must be ascertained. If the hydrogen ion concentration of a solution is known then the pH of a solution can be calculated by using the formula-

$$pH = \log (1/H^+).$$

Determination of pH of water with the help of law of mass action :

Water dissociates to a small but definite extent, depending on the temperature. i. e. $HOH = H^+ + OH^-$.

The higher the temperature, greater will be the dissociation.

According to the law of mass action, at equilibrium-

$$\frac{(H^+) \times (OH^-)}{(HOH)} = K \text{ (Constant)}$$

But ordinarily, very few water molecules in a mass of water may get dissociated; So, the vast mass of undissociated water may taken to remain constant.

Thus -

$$\frac{(H^+) \times (OH^-)}{(HOH)} = K$$

or $(H^+) \times (OH^-) = (HOH) \times K$

$= K_1 \times K$

$= K_W$.

Here K_W is ion product or dissociation constant of water at particular temperature. At room temperature (25^0C) the value of $K_W = 1 \times 10^{-14}$ gmEq./Liter.

As dissociation of each molecule of water yields equal numbers of H^+ and OH^-

$$\text{So } (H^+) \times (OH^-) = K_W$$
$$\text{or, } (H^+) \times (H^+) = 1 \times 10^{-14}$$
$$\text{or, } (H^+)^2 = 1 \times 10^{-14}$$
$$\text{or, } H^+ = -1 \times 10^{-7}$$
$$\text{As pH} = -\log (H^+)$$
$$\text{So, pH} = -\log (10^{-7})$$
$$= 7$$
$$\text{So, pH of water} = 7.$$

Q. ***Why water is taken as standard for comparison of pH?***

Ans.

i. Water Dissociates to a small but definite extent, depending on the temperature.
ii. It produces same amount of H^+ and OH^- when dissociate.
iii. It is neutral in nature.
iv. It is stable and do not change physically and chemically for a long range of variation.

So, Water is taken as standard for comparison of pH.

pOH

It is the negative logarithm of (OH^-) ion concen-tration of a solution. It is useful in calculating the pH of an alkaline solution.

Safe guard of pH

1. 1st line :
   i. Buffers - within seconds
   ii. Respiratory system - minute to hours.
2. 2nd line :
   i. Kidney system - hours to days.

Metabolic acid base production :

1. Volatile acid (CO_2) : 12 - 18 mole/day
2. Non-volatile acid : 50 - 100 meq/day (1 meq/kg/day)
3. Total acid : 1240 meq/day
4. Total base : 1160 meq/day
5. NET acid : 80 meq/day.

Routes of acid excretion :

1. Lungs : volatile acid
2. Kidney : non-volatine acid.

N.B. Buffers are giving important protection of our pH system from production to excretion.

Buffer

Definition : Buffer is the mixture of weak acid and it's salt with strong bases (B^-/HB)

Example :

i. $NaHCO_3$ / H_2CO_3
ii. KHb / H-Hb or $KHbO_2$/ H-HbO_2
ii. Na_2HPO_4 / NaH_2PO_4
iv. Prot. / H-prot.
v. NH_3 / NH_4^+

It depends upon-

a. pK of the buffer.
b. Concentration of buffer substance.

$$\text{pH of a buffer solution, pH} = \text{pK} + \log \frac{\text{salt (anti-acid compert)}}{\text{acid (anti-base compert)}}$$

Composition of buffer : It is a pair of weak acid and its salt with a strong base.

Importance of buffer :

i. It maintain the constant hydrogen ion concentration of the body for optimum cellular activity.
ii. It is important in maintenance of normal acid-base balance of the body.
iii. It is important for the optimum activity of enzyme.

Buffer solution

A solution of two or more chemical compounds which has the ability to accept either the (H^+) or (OH^-) ions, in the solution, thus maintaining the pH of the solution relatively constant, despite the addition of considerable quantity of acid and base.

Physiological buffer :

These are the buffers present in the body and maintains the pH of body fluid at a constant level, despite the addition of acid and alkali produced during metabolic activity is called physiological buffer. Example : H_2CO_3/HCO_3^-.

Buffer system of the body

Buffer system of the body are *(according to severity)* :

1. *Plasma buffers :*
   i. Bicarbonate buffer : $NaHCO_3$ / H_2CO_3
   ii. Protein buffer : Prot. / H-Prot.
   ii. Phosphate buffer : Na_2HPO_4 / NaH_2PO_4
2. *RBC buffers :*
   i. Haemoglobin buffer : KHb / H-Hb *or* $KHbO_2$/ H-HbO_2
   ii. Bicarbonate buffer : $NaHCO_3$ / H_2CO_3
   iii. Phosphate buffer : Na_2HPO_4 / NaH_2PO_4
3. *Blood buffers :*
   i. Bicarbonate buffer : $NaHCO_3$ / H_2CO_3
   i. Haemoglobin buffer : KHb / H-Hb or $KHbO_2$/ H-HbO_2
   iii. Protein buffer : Prot. / H-Prot.
   iv. Phosphate buffer : Na_2HPO_4 / NaH_2PO_4
4. *ECF buffers :*
   i. Bicarbonate buffer : $NaHCO_3$ / H_2CO_3
   ii. Phosphate buffer : Na_2HPO_4 / NaH_2PO_4
   iii. Protein buffer : Prot. / H-Prot.
5. *ICF buffers :*
   i. Protein buffer : Prot. / H-Prot.
   ii. Phosphate buffer : Na_2HPO_4 / NaH_2PO_4
   iii. Bicarbonate buffer : $NaHCO_3$ / H_2CO_3
6. *Systemic buffers :*
   a. Acting throught the respiratory system :
      i. Oxidised and reduced haemoglobin buffer system
      ii. HCO_3^-/H_2CO_3 buffer system.
   b. Acting through urinary system :
      i. Phosphate buffer system (NaH_2PO_4 / $Na_2H\ PO_4$)
      iv. Ammonia buffer system (NH_3 / NH_4^+).

Buffering capacity

Means the capability of resisting the change in pH by accepting either the (H^+) or (OH^-) ions.

Total body buffering capacity :

1000 meq H^+/OH^- or 12-15 meq/kg.

i. Bicarbonate buffer ($NaHCO_3$ / H_2CO_3) : 55 %
ii. Haemoglobin buffer (KHb / H-Hb *or* $KHbO_2$/ H-HbO_2) : 35 %
iii. Protein buffer (Prot. / H-Prot.) : 5 %
iv. Phosphate buffer (Na_2HPO_4 / NaH_2PO_4) : 5 %

Body buffering activity :

1. *ECF buffer* : Quick action, low capacity-
   i. Bicarbonate buffer ($NaHCO_3$ / H_2CO_3) : 86 %
   ii. Protein buffer (Prot. / H-Prot.) + Phosphate buffer (Na_2HPO_4 / NaH_2PO_4) : 14 %
1. *ICF buffer* : Delayed effect, high capacity, affect plasma K^+ level.
   i. Protein buffer (Prot. / H-Prot.) + Phosphate buffer (Na_2HPO_4 / NaH_2PO_4) : 64 %
   ii. Bicarbonate buffer ($NaHCO_3$ / H_2CO_3) : 36 %

pK

Is the negative logarithm of dissociation constant.

pK of body buffers :

i. $NaHCO_3$ / H_2CO_3 : 6.1
ii. KHb / H-Hb or $KHbO_2$/ H-HbO_2 : 6.5 - 7.8
ii. Na_2HPO_4 / NaH_2PO_4 : 6.8
iv. Prot. / H-prot. : 6.5 - 7
v. NH_3 / NH_4^+ : 9.0

Buffering capacity will maximum when, pK = pH

Q. When will be the pH = pK?

Ans. We know that pH = pK + log (Salt/Acid).
If the ratio of salt to acid is 1 : 1 (i.e. concentration of salt and acid is same). Then the pH of the resultant mixture would be equal to pK.

Mode of buffer action :

i. Conversion of strong acid into weak acid.
ii. Conversion of strong base into neutral salt.

Mechanism of buffer action :

Buffer posses the capability of resisting the change in pH, by accepting either the (H^+) or (OH^-) ion.

So when strong acid such as HCl is added in bicarbonate buffer system (H_2CO_3/$NaHCO_3$), then $NaHCO_3$ neutralizes it, and strong acid is converted into weak acid.

$$HCl + NaHCO_2 = NaCl + H_2CO_3 \text{ (weak acid)}$$

Similary when a strong base such as NaOH is added in same buffer system (H_2CO_3/$NaHCO_3$), then H_2CO_3 converted the NaOH into neutral salt.

$$H_2CO_3 + NaOH = NaHCO_3 \text{ (Neutral salt.} + H_2O)$$

Differnce between bicarbonate and phosphate buffer

Trait	*Bicarbonate buffer*	*phosohate buffer*
1. Composition	$NaHCO_3$ / H_2CO_3	(Na_2HPO_4 / NaH_2PO_4
2. Conc. ratio in blood	20/1	4/1
3. Blood conc.	26-28 mmol/L High concentration	1.0 mmol/L Low concentration
4. Linked up with	Respiratory & kidney system	Kidney system
5. Defence	1st line of defence	less effective
6. pK	It is weaker than phosphate buffer because its pk is away fromthe pH of ECF	It is stronger than bicar bonate buffer because its pk is nearer to the pH of ECF
7. Importance	In ECF because of greater concentration	In ICF because of greater concentration.

Importance of bicarbonate buffer :

It plays an important role in the maintanence of acid-base balance because the concentration of each of the two element of the system can be regulated.

i. CO_2 is regulated by respiratory system.
ii. Bicarbonate ion by the kidney.

Bone buffer

i. Alkaline calcium salt of bone
ii. Capacity : 35000 meq H^+ (adult)
iii. $Ca_3(PO_4)_3 + Ca^{++} + H_2O \longleftrightarrow Ca_{10}(PO_4)_6(OH)_2 + H^+$

Hydroxy appatite crystal

Hydroxy appatite crystal → pick up proton (H^+).

iv. Chronic acidosis :
In chronic renal failure → bone buffer acts to maintain H^+ concentration.
   a. During alkalosis : by releasing proton (H^+)
   b. During acidosis : by picking up proton (H^+)

Total buffer base

Total buffer base of blood = 48 meq/L

i. HCO_3^- : 28 meq/L
ii. Hb^- : 15 meq/L
ii. Others : 5 meq/L

Base excess (BE) :

Base excess = Observe buffer base (HCO_3^- concentration) - normal buffer base (normal HCO_3^- concentration)

Normal value of base excess : -2 to +2 meq/L

i. +ve base excess : Metabolic alkalosis
ii. -ve base excess : Metabolic acidosis

N.B. Base component of a buffer fight against proton (H^+)

Acid base disorder

Types of acid base disorder :

1. *Simple acid base disorder* :
   i. *Metabolic*
      a. Acidosis (decrease HCO_3^-)
      b. Alkalosis (increase HCO_3^-)
   ii. *Respiratory*
      a. Acidosis (increase PCO_2)
      b. Alkalosis (decrease PCO_2)
2. *Complex acid base disorder* : If both component vary. Any combination of 4 simple acid base disorder, but all four can not persist in a body.

Acid base parameters

1. Classical acid base parameters
   i. pH (7.4)
   ii. PCO_2 (40 mm of Hg)
2. Non classical acid base parameters
   i. Plasma anion gap
   ii. Electrolytes.

Plasma anion gap :

Law of neutrality-
Cations = Anions

i.e $Na^+ + K^+$ + unmeasured cations (UC)
= $Cl^- + HCO_3^-$ + unmeasured anions (UA)

$(Na^+ + K^+) - (Cl^- + HCO_3^-)$
= Unmeasured anions - unmeasured cations
= UA - UC
= Anion gap

UC : Ca++, Mg++, gama globulin

UA : Plasma protein, SO_4, PO_4, lactate, others

Normal value : 12 (+/-) 4 meq/L.

Causes of increased anion gap :

i. Renal failure
ii. Lactic acidosis
iii. Ketoacidosis
iv. Intoxication of aspirin, alcohol poisoning.

N.B. End product of alcohol metabolism → organic acid → anion of that organic acid → increase anion gap).

Compensatory mechenism of acid baes disorder

1. Metabolic acidosis :

$$= \frac{\textit{decreased } HCO_3^-}{PCO_2}$$

$$\text{Compensation} = \frac{\text{decreased } HCO_3^-}{\text{decrease } PCO_2}$$

→ pH becomes normal,
but total body CO_2 decreases due to * *hyperventilation*
(Respiratory sysrem managed)

2. Metabolic alkalosis :

$$= \frac{\textit{increased } HCO_3^-}{PCO_2}$$

$$\text{Compensation} = \frac{\text{increased } HCO_3^-}{\text{increase } PCO_2}$$

→ pH becomes normal,
but total body CO_2 increases due to * *hypoventilation*
(Respiratory sysrem managed)

1. Respiratory acidosis :

$$= \frac{HCO_3^-}{\textit{increased } PCO_2}$$

$$\text{Compensation} = \frac{\text{increase } HCO_3^-}{\text{increased } PCO_2}$$

→ pH becomes normal,
but total body CO_2 increases due to * *HCO_3^- generation* by the kidney
(Kidney sysrem managed).

4. Respiratory alkalosis :

$$= \frac{HCO_3^-}{\textit{decreased } PCO_2}$$

$$\text{Compensation} = \frac{\text{decrease } HCO_3^-}{\text{decreased } PCO_2}$$

→ pH becomes normal,
but total body CO_2 decreases due to * *increase HCO_3^- excretion* by the kidney
(Kidney sysrem managed).

4 sequele occurs :

1. Total body CO_2 decreases in-
   i. Metabolic acidosis
   ii. Respiratory alkalosis
   iii. Metabolic acidosis + Respiratory alkalosis.
2. Total body CO_2 increases in-
   i. Metabolic alkalosis
   ii. Respiratory acidosis.
3. Total body CO_2 normal with acid baes disorder in-
   i. Metabolic acidosis + Respiratory acidosis
   ii. Metabolic alkalosis + Respiratory alkalosis.
4. Total body CO_2 normal with acid baes disorder in-
   i. Metabolic acidosis + Metabolic alkalosis.

Laws & Equation

Law of mass action :

The velocity of reversible reaction is directly proportional to the product of the concentration of the reacting mass at constant temperature.

Chemical reaction :

$$HOH \underset{V_2}{\overset{V_1}{\rightleftharpoons}} H^+ + OH^-$$

According to the law of mass action the velocity (V_1) of Ist reaction is proportional to (HOH) ie.

$V_1 \propto (HOH)$ or

$V_1 = K_1 (HOH)$ i

Here, K_1 is constant.

When velocity (V_2) of 2nd reaction is considered

$V_2 \propto (H^+) \times (OH^-)$ or

$V_2 = K_2 (H^+) \times (OH^-)$ ii

Here, K_2 is constant.

The velocity of reactions i & ii are equal as the reaction occur at equilibrium position i.e.

$V_1 = V_2$

i.e.

$K_1(HOH) = K_2 (H^+) \times (OH^-)$

or $\frac{K_1}{K_2} = \frac{(H^+) \times (OH^-)}{HOH} = K$

or $\frac{(H^+) \times (OH^-)}{HOH} = K = \frac{\text{Dissociated water}}{\text{Undissociated water}}$

Here, K is equilibrium constant .

Importance of Law of mass action :

It is used to determine -

i. The p^H of a solution.
ii. The hydrogen ion concentration (H^+).
iii. The dissociation constant.
iv. Handerson-hasselbalch reaction.

Handerson-Hasselbalch Equation

Definition : The relationship between pH, pK and the concentration of an acid and its salt can be stated by a convenient equation -

$$p^H = p^K + \log \frac{\text{salt}}{\text{acid}}$$

This equation is called Handerson-Hasselbalch equation.

Here, pK is the negative logarithm of dissociated constant .

Explanation : When considered a pure solution of a weakly dissociated acid at equilibrium stage.

Such as $HB \longleftrightarrow H^+ + B^-$ *(B^- = Base)*

According to the *low of mass action :*

$$\frac{(H^+) \times (B^-)}{(HB)} = K \qquad \textit{(K= equilibrium constant)}$$

So,

$$(H^+) \times (B^-) = K\,(HB) \qquad \textit{(Cross multiplication)}$$

$$(H^+) = K \frac{(HB)}{(B\text{-})} \qquad \textit{(Divided each side by } B^-\textit{)}$$

$$\textit{So, } \text{Log}\,(H^+) = \log \frac{K\,(HB)}{(B^-)}$$

$$\text{or, } \log (H^+) = \log K + \log \frac{(HB)}{(B^-)}$$

$$\textit{So, } -\log (H^+) = -\log K - \log \frac{(HB)}{(B^-)}$$

$$\text{or, } -\log (H^+) = -\log K + \log \frac{(B^-)}{(HB)}$$

$$\text{or, } \quad pH = pK + \log \frac{(B^-)}{(HB)}$$

$$pH = pK + \log \frac{\text{Salt}}{\text{acid}}$$

Importance of Handerson-Hasselbalch equation :

1. It is used to determined the pH of a buffer solution.
2. For determination of the relative concentration of salt and acid required.
   a. pK = pH, when the two constituents are present in equal concentration.
   b. pH of buffer solution is determined by the ratio of salt and acid.
   c. The buffering power of a substance is highest when pH = pK.

Donan Equilibrium

Definition : It is the condition of unequal distribution of diffusible ions across the semipermeable membrane due to the presence of non diffusible anion on one side of the semipermeable membrane.

Importance of Donnan equilibrium :

1. It explains how difference of electrical potential can be established on two sides of a membrane.
2. It may also involved in absorption and secretion.
3. In maintenance of differential concentration between the various compartments of the body.
4. Phenomenon of chloride shift can also be explained from this standpoint.

Explanation *:* Consider two ionized solutions a and b filling compartments of constant volume and separated by a partially permeable membrane. It was shown theoretically by Gibbs and confirmed experimentally by Donnan-
that, *at equilibrium* :

1. Each solution will be electrically neutral- it's total charges on cations will equal those on anion.
2. The product of the diffusible ion on one side of the membrane will equal the product of the diffusible ions on the other.

$$(\text{Diffusible cations})_a \times (\text{Diffusible anions})_a = (\text{Diffusible cations})_b \times (\text{Diffusible anions})_b$$

From which it follows that -

$$\frac{(\text{Diffusible cations})_a}{(\text{Diffusible cations})_b} = \frac{(\text{Diffusible anions})_b}{(\text{Diffusible anions})_a}$$

Consider that in our simple system sodium chloride (Na^+Cl^-) is present in solution *a* and *b* but that only *a*, contains a salt (Na^+X^-); where X^- is an undiffusible anion unable to cross the membrane.

Thus -

	Na^+	Na^+
Solution (a)	Cl^-	Cl^- *Solution (b)*
	X^-	

The penetrating ions (Na^+ and Cl^-) diffuse until equilibrium is attained. The two criteria established above will hold, namely.

$$(Na^+)_a = (Cl^-)_a + (X^-)_a \qquad \textit{Electrically Neutral}$$

$$(Na^+)_b = (Cl^-)_b$$

and

$(Na^+)_a \times (Cl^-)_a = (Na^+)_b \times (Cl^-)_b$

Products & ratio of diffusible ions

or, $\frac{(Na^+)_a}{(Na^+)_b} = \frac{(Cl^-)_b}{(Cl^-)_a}$

From these relationships it follows that-

$(Na^+)_a > (Cl^-)_a$

and therefore-

$(Na^+)_a > (Na^+)_b$

$(Cl^-)_a < (Cl^-)_b$

and

$(Na^+)_a = (Cl^-)_a + (X^-)_a > (Na^+)_b + (Cl^-)_b$

So,

1. Cation concentration on the side containing non-diffusible anion will greater that on the other side.
2. Anion (diffusible) concentration will be more on the side without non-diffusible anion.
3. Side containing non-diffusible ion will have more negativity.

(Ref. wright's)

Indicator

Definition : Indicator is the weak acid or weak base which indicates the acid-base reaction by changing their colour in an ionized and unionized form. It also indicates the end point of a reaction.

They react by changing their colour in an ionized and unionized form.

Some Common idicators with pH :

Indicator	*pH range*	*Colour change*
1. Topfer's reagent	2.9 - 4.0	Red to yellow
2. Methyl red	4.2 - 6.3	Red to yellow
3. Litmus	4.5 - 8.3	Red to blue
4. Phenopthalein	8.3-10.0	Colourless to Red
5. Phenol red	6.6 - 8.3	Yellow to red

Use of indicator :

i. It is used to determine the pH of a solution.
ii. It also used in the laboratory for the titration, to indicate the end point of an acid-base reaction.

Q. ***How indicator is chosen?***

Ans. Indicator is chosen according to the pH of media and the pK of indicator.

Titration

Titration is the process by which the concentration of a solution is determined against (by) a known solution with the help of indicator.

Importance of titration : The process is used in the laboratory to know the strength and concentration of unknown solution.

Biological Oxidation

Oxidation : Addition of oxygen or removal of hydrogen or removal of electron with gaining valency is called oxidation or chemical oxidation.

Reduction : Loss of O_2 and addition of H^+ or electrons is known as reduction.

N.B. The enzymic actions are activated by the presence of some accessory substances. When these accessory substances are single ions (Mg^+, PO_4^-), they are called *co-factors*, but when they are complex non-protein organic molecules, they are known as *co-enzymes.*

Biological Oxidation : Oxidation in the tissue cells is called biological oxidation.

Difference between oxidation and biological oxidation :
Oxidation occurs only one step of reaction . Biological oxidation occurs through several steps of reaction.

Oxido-reductases

Enzymes that carry out biological oxidation are known as oxido-reductases. They are classified into five groups.

1. *Oxidase :* They catalyses the removal of H_2 but uses only O_2 as hydrogen acceptor.
   Example : Cytochrome oxidase. phenolase, lactase etc.
2. *Aerobic dehydrogenase :* They catalyses the removal of H_2 but uses either O_2 or methyle blue, (artificial substances) as hydrogen aceptor.
   Example : D-amino-acid oxidase, L-amino-acid oxidase
3. *Anaerobic dehydrogenase :* They catalyses the removal of hydrogen but can not use O_2 as hydrogen acceptor.
4. *Hydroperoxidase :* These enzymes use H_2O_2 as their substrate.
5. *Oxygenase :* They catalyzes the direct transfer and incorporation of oxygen into substrate molecule.

Q. ***Why many steps of reaction is required for biological oxidation?***

Ans. If biological oxidation occurs through one step of reaction , tremendous energy is released which is not tolerable for the cell and it will destroy the cell. So many steps of reaction is required.

Q. ***Where ATP is formed in biological oxidation reaction?***

Ans. In three sites ATP is formed :

i. Between $NADH_2$ and FAD, where $NADH_2$ released H_2 which received by FAD.
ii. Between the cytochrom B and C
iii. Between the cytochrome A and A_3.

Oxidative phosphorylation

The transfer of hydrogen to flavoprotein is associated with the formation of ATP from ADP and the further transfer along the flavoprotein-cytochrome system generates 2 more molecules of ATP per pair of proton transfered. This production of ATP coupled to oxidation is called oxidative phosphorylation.

Enzyme

Definition : Enzymes are protein catalists that increase rate of reactions without themselves being changed in the overall process.

(Ref. Lippincott's illustrated reviews of Biochemistry 2nd, P-47)

or Enzyme are organic catalysts, produced by the living cells. They only accelarates the reaction not decrease the reaction.

But inorganic catalyst increases or decreases the reaction.

Enzymes are protein in nature.

Properties of enzymes :

i. Enzymes are heat liable.
ii. Enzymes are made up of protein.
iii. It is not dialysable.
iv. Enzymes remain unchanged after reaction.
v. Specificity of enzyme.

Q. *Why enzymes are not dialysable?*

Ans. Enzymes are made up of proteins. As proteins can not dialysed. So enzymes are not dialysable.

Enzymes specificity :

The enzymes are specific in their reaction. One enzymes can act only on a particular type of substrate just as key fits for a particular lock. e.g. amylase acts on starch, lipase acts on lipids etc.

Stability of enzyme depends upon :

i. pH
ii. Temperature
iii. Concentration of solution.

Mechanism of enzyme action :

According to Michaelis and Menten-

i. Enzyme (E) molecule first combine with the substrate (S) to form transient enzyme-substrate complex (ES).
ii. It is a loose complex, but not a proper compound.
iii. The complex soon dissociates to liberate a new substance (i.e. product, P) and the enzyme remains unchanged.

$$E + S \longleftrightarrow ES \longrightarrow E + P$$

Q. ***Why enzyme produces continually?***

Ans. After reaction enzyme becomes old and is not sufficient for further reaction. Then renewal of enzyme or new set of enzyme are must required. For this reason enzymes are produced continually.

Substrate : Substance which may be acted upon by an enzyme are called substrate of that enzyme.

Classification of enzyme :

Enzymes are broadly classified into six major classes according to the types of reaction catalyzed by them. These are -

1. *Oxidoreductases* : Catalyze oxidation-reduction reactions.
   Example : *Lactate dehydrogenase*- Oxidised lactic acid to pyruvic acid.

   $$\text{Lactate} + NAD^+ \longleftrightarrow \text{Pyruvate} + NADH + H^+$$

2. *Transferases* : Enzymes of this class catalyze the transfer of a particular group (C, N or P-containing group) from a molecule of one substrate to a molecule of another substrate.
   Example :
   i. *Transaminase*
   ii. *Serine hydroxy-methyl transferase* etc.
   $$\text{Serine} + THF \longleftrightarrow \text{Glycine} + THF^{--}CH_2$$

3. *Hydrolases* : These enzymes catalyze the breakdown of their substrates by hydrolysis i.e cleavage of bonds by addition of water.
   Example :
   i. *Amylase, lipase, pepsin, *urease* etc which causes hydrolysis of food stuffs.
   ii. $\text{Urea} \longleftrightarrow CO_2 + 2H_2O$

4. *Lyases* : Catalyze cleavage of C-C, C-S and certain C-N bonds.
   Example :
   i. Carbonic anhydrase catalyses H_2CO_3 to split it into water and carbondioxide.
   ii. *Pyruvate decarboxylase* :
   $$\text{Pyruvate} \longleftrightarrow \text{Acetaldehyde} + CO_2$$

5. *Isomerases :* These are the enzyme that catalyzes the interconversion of different isomers.
   Example :
   i. *Glucose phosphate isomerase*- which converts Glucose-1-P into Glucose -6-P and vice versa.
   ii. *Methylmalonyl CoA mutase* :
   Methylmalonyl CoA $\longleftrightarrow$ *Succinyl CoA*

6. *Ligases :* The enzymes that are capable of binding together of two molecules are known as ligases or synthetase i.e catalyze formation of bonds between carbon and O, S, N coupled to hydrolysis of high-energy phosphates.
   Example :
   i. *Citrate synthetase*
   ii. *Pyruvate carboxylaase :*
   $$\text{Pyruvate} + CO_2 \longleftrightarrow \text{Oxaloacetate}$$

(Ref. Lippincott's illustrated reviews of Biochemistry 2nd, P-47)

Zymase secretion

Some extracellular enzymes secreted in active form called zymase secretion.

Example : Ptyaline of saliva.

Zymogen secretion

Many enzymes are quite inactive when they are freshly secreted, called zymogen secretion. They require to be activated by other substances.

Example : Pepsinogen, trypsinogen etc.

Anti-enzyme

The substances, produced as a result of repeated injection of

certain enzymes in the serum, which prevents the normal activity of particular enzyme.

Example : Antipepsin, Antitripsin etc.

Isoenzyme

Iso-enzymes are the multiple forms of a same enzyme. They are physically distinct form of the same catalytic activity. Thus they catalyze the same reaction. So they are called isoenzyme (*also called isozymes*).

Example : Creatinine kinase (CK), lactate dehydrogenase (LDH), Glutamate:oxaloacetate transaminaes (GOT). These are commonly used in the diagnosis of *myocardial infarction.*

Many isoenzymes contain different subunits in various combinations. For example, creatine kinase occurs as three isoenzymes-

i. $CK_1 = BB$
ii. $CK_2 = MB$
iii. $CK_3 = MM$.

Importance :

i. Diagnosis of myocardial infarction :
   a. CK2 : Following a myocardial infarction, this isoenzymes appears approximately 4 to 8 hours following onset of chest pain, and reaches a peak in activity at approximately 24 hours.
   b. Lactate dyhydrogenase : Activity is also elevated in plasma following an infarction, peaking 3 to 6 days after the onset of symptoms. LDH activity is thus of diagnostic value in patients admitted more than 48 hours after the infarction- a time period when plasma CK2 may provide equivacal results.

(Ref. Lippincott's illustrated reviews of Biochemistry 2nd, P-59)

Enzyme modifier

The factors which influence or modifies the activity of the enzyme is called enzyme modifier and the reaction is called the enzyme modification reaction. There are two types of modifiers

i. *Positive modifiers :* The factors which increases the catalytic activity of the enzyme. *Example* : Fe^{++}, Mg^{++} etc.
ii. *Negative modifiers :* The factors which decreases the catalytic activity of the enzyme.

Factors influence the enzyme activity

1. *Enzyme concentration :* More is the enzyme, more is the reaction and more will be the velocity of reaction.
2. *Substrate concentration :* Up to a certain point if the substrate concentration is increased, the speed of enzyme activity is also increased.
3. *P^H :* Which influences tremendously the chemical reaction of enzyme activity.
4. *Temperature :* Within limitation, more is the temperature more is the reaction. (30-40)°C works very efficiently.
5. *Influence of metabolic ions :* Many enzymes are inactive unless a cation (magnesium, calcium, zinc etc) is present.
6. *Effect of hormones :* Many hormones can influence the enzyme activity. For example epinephrine and glucagone enhance the production of cyclic AMP in the liver cells, the cyclic AMP inturn promotes the convertion of enzyme phosphorylase to its active form.
7. Presence or absence of co-enzyme or co-factors.

Types of enzyme inhibitor

Enzyme inhibitor falls in two groups :

1. *Compititive inhibitor :* Those which has structural similarity with the substrate molecule for the active site of the enzyme.
2. *Non compititive inhibitor :* Those which are attached not to the active site of the enzyme but to some other site of the enzyme.

Co- Enzyme

Dfinition : Co-enzymes are a group of chemical substance which are independent in their function. They are the non-protein prosthetic part of the enzyme.

Example : NAD^+, FAD^+, $NADP^+$, CoA etc.

The properties of co-enzyme are :

i. Heat stable
ii. Dialysable
iii. Non-colloidal
iv. Non protein.

Apo-enzyme

The protein part of an enzyme is called apoenzyme.

Holoenzyme

The composite enzyme molecule consisting of the apo-enzyme and the co-enzyme is called holoenzyme.

Co-factors

Co-factors are the divalent metalic ions. These are accessory substance, non-protein in nature which are neccssary for accelerate the enzyme reaction in addition to co-enzyme. Ex. Mg^{++}, Ca^{++} etc.

Co-enzyme A

The co-enzyme form of pantothanic acid is called co-enzyme A. It is biologically important as it carries or donates acetyl group with sulfhydril group.

***Difference between the* enzyme & co-enzyme**

Enzyme	*Co-enzyme*
1. Enzymes are organic catalyst.	1. Co-enzymes are accessory substances.
2. It is protein in nature.	2. It is non protein in nature.
3. Enzyme is not dialysable.	3. Co-enzyme is dialysable.
4. Heat and pH liable.	4. Heat and pH stable.
5. Enzyme can act itself.	5. It is required by an enzyme for its catalytic reaction.

Osmosis

Definition :

Migration of solvent from the solution of lower concentration to the higher concentration, when they are seperated by a semipermeable membrane is *called osmosis.*

Rate of osmosis depends upon:

i. Difference in osmotic pressure of the solution.
ii. Permeability of the membrane.
iii. Electrical potential across the membarane and charge upon the wall and pore of the membrane.

Osmotic pressure :

Definition :

The force (pressure) by which the osmosis occurs is called osmotic pressure.

Physiological importance :

i. Absorption from the intestine.
ii. Exchange in the capillary bed.
iii. Regulation of urine formation.
iv. Contineous osmotic exchange between plasma and red cells.
v. Clinical use : Injection of saline are given by way of treatment.

Q. *On which factors osmotic pressure depends and why?*

Ans.

Osmotic pressure depends upon the total number of the particles per unit volume but not upon the size of the molecules.

Because each particle in a solution exerts, on the average, the same amount of pressure against the membrane.

Q. ***Do you think crystaloid particles exert more osmotic pressure than colloid particles, why?***

Ans.

Yes, crystaloid particles exert more osmotic pressure. Because, ionisable particle exert more osmotic pressure than non-ionised particles.

Q *Why ionise particle exert more Osmotic pressure than non-ionised particles?*

Ans.

A substance, which ionises has more number of osmotic particle, so osmotic pressure of ionised substance is more than of non-ionised substance.

Relation between osmolality to osmotic pressure

At nomal body temperature, 1 milliosmole per liter concentration is equivalent to 19.3 mm Hg of osmotic pressure.

So, osmotic pressure (mm Hg) = 19.3 x osmolality
(milli osmole /L).

Diffusion

Definition : The continual movement of molecules in a solution from a higher concentration to lower concentration is called diffusion.

Diffusion depends : Diffusion depends upon the weight and size of the molecules.

Physiological importance of diffusion :

i. Admixture of food stuffs with digestive juice.
ii. Absorption from the intestine.
iii. Exchange between plasma and red cells.
iv. Exchange in the capillary bed.
v. Admixture of gases in the lungs.

Factors affect the rate of diffusion :

1. *Concentration gradient :* The greater the concentration difference, the greater is the rate of diffusion.
2. *Molecular diameter :* The less the diameter of the molecule, the greater is the rate of diffusion.
3. *Distance between the area :* The shorter is the distance, the greater is the rate of diffusion.
4. *Cross section :* The greater the cross section of the chamber in which the diffusion is taking place, the greater is the rate of diffusion.
5. *Temperature :* The greater the temperature, the greater is the rate of diffusion.

$$\text{Diffusion rate} = \frac{\text{Concentration difference x cross sectional area x temperature}}{\sqrt{\text{Molecular weight x distance}}}$$

Types of diffusion :

i. *Simple diffusion :* Some lipid soluble substances (O_2, CO_2, alcohol, and fatty acids. can easily diffuse through the cell membrane, called simple diffusion. Here carrier is not required.
ii. *Facilitated diffusion :* Some lipid insoluble substance (glucose etc) can diffuse through the lipid matrix of cell membrane with the help of carrier mechanism called facilitsated diffusion. Here carrier is required.

Factors essential for facilitated diffusion

1. Concentration gradient
2. Amount of carrier
3. Enzyme.
4. The rapidity with which the chemical reaction involved in the mechanism takes place.

Difference between the simple and facilitated diffusion

Simple diffusion	*Facilitated diffusion*
1. Carrier is not needed.	1. Carrier must be present.
2. Rate of diffusion is almost exactly proprtional to the difference of the concentration of particle on the two side of the membrane.	2. For a carrier transported substance, rate of diffusion approches a maximum, as the concentration of the substance increase.

Difference between the diffusion & osmosis

Diffusion	*Osmosis*
1. Movement of the solute particles take place.	1. Movement of the solvent particle take place.
2. Movement of solute occurs from higher to lower. concentration.	2. Movement of solvent from lower to higher concentration.
3. Semipermeable membrane may or may not present.	3. Semipermeable membrane must be present.
4. It depends upon the wt. & size of the solute perticles.	4. It depends upon the number of particles per unit volume of solution.

Transport

Difinition : It is the bio-physiochemical phenomenon by which different substance are transported from one place to other place in our body.

Types of transport :

1. Active Trnasport
2. Passive Transport

Active Transport

The movement of substance across the cell membrane against the concentration gradient with active expenditure of energy by the help of carrier called active transport.

The energey is derived from ATP and the carriers are present in the cell membrane.

Each type of carrier transports only a specific substance.

The gradient may be :

i. Electrical.
ii. Pressure.
iii. Concentration
iv. Speed of flow.

Active transport generally requires :

i. Active expenditure of energy
ii. Special carrier system
iii. Difference of concentration gradient
iv. Enzymes.

Types of active transport -

i. Primary active transport.
ii. Secondary active transport.
   a. Co-transport
   b. Counter transport.

Active transport is divided into two types according to the source of the energy used to cause the transport. They are called primary active transport and secondary active transport.

(Ref. Guyton & Hall- 11th Edition; Page-52)

Primary Active Transport

In primary active transport, the energy is derived directly from the breakdown of adenosine triphosphate (ATP) or some other high energy phosphate compound. Transport depends on carrier proteins that penetrate through the membrane ie Na^+-K^+ pump.

(Ref. Guyton & Hall-11th Edition; Page-53)

Na^+-K^+ Pump

Sodium-potassium pump refers to the mechanism that transports sodium ions out of the cells to the exterior and at the same time pumps potassium ions from the outside to the inside. Here two K^+ ions are transferred for each three Na^+ ions.

Explanation :

The carrier protein of the N^+-K^+ pump is a complex of two separate globular proteins, a larger one (molecular weight 100,000) and a smaller one (molecular weight 45,000). The function of the smaller protein is not known. *The larger protein has three specific features that are important for function of the pump* :

i. It has three receptor sites for binding sodium ions on the portion of the protein that protrudes to the interior of the cell.
ii. It has two receptor sites for potassium ions on the outside.
iii. The inside portion of this protein adjacent to or near to the sodium binding sites has ATPase activity.

When 3 Na^+ ions bind on the inside of the carrier protein and 2 K^+ ions on the outside, the ATPase function becomes activated. This then leaves 1 molecule of ATP, splitting it to ADP and liberating a high energy phosphate bond of energy. This energy is then believed to cause a conformational change in the protein carrier molecule, extruding the sodium ions to the outside and potassium ions to the inside.

Importance of Na^+-K^+ pump : This pump is responsidble for-

i. Maintaining the sodium and potassium concentration difference across the cell membrane
ii. Establishing a negative electrical potential inside the cells.
iii. The pump is so imprtant to many different functioning systems of the body such as to nerve & muscle fibres for transmission of impulses, various glands for the secretion of different substances, and all the cells of the body to prevent cellular swelling.

(Ref. Guyton & Hall- 11th Edition; Page-53, 54)

Primary active transport of calcium : Calcium ions are normaly maintained at extremely low concentration in the intracellular cytosol of virtually all cells in the body, at concentration about 10,000 times less than that in the extracellular fluid. This is achieved mainly by two primary active transport calcium pumps. *One* is in the cell membrane and pumps calcium to the outside of the cell. The *other* pumps calcium ions into one or more of the internal vesicular organelles of the cell such as into the sarcoplasmic reticulum of muscle cell and into the mitochondria in all cells. In each of these instances, the carrier protein penetrates the membrane from side to side and also serves as an ATPase, having the same capability to cleave ATP as the ATPase sodium carrier protein.

The difference is that this protein has a highly specific binding site for calcium instead of sodium.

(Ref. Guyton & Hall- 11th Edition; Page-54)

Primary active Transport of Hydrogen ions :

At two places in the body are important primary active transport systems for hydrogen ions. They are -

1. In the gastric glands of the stomach .
2. In the late distal tubules and cortical collecting ducts of the kidneys.

In the gastric glands, the deep-lying parietal cells have the most potent primary active mechanism for transporting hydrogen ions of any part of the body. This is the basis for secreting hydrochloric acid in the stomach digestive secretions. At the secretory side of the parietal cells, the hydrogen ion concentration can be increased as much as a million fold and then released in association with chloride ions in the form of hydrochloric acid.

In the renal tubules there are special intercalated cells in the late distal tubules and cortical collecting ducts that also transport hydrogen ions by primary active transport. In this case, large amounts of hydrogen ions are secreted into the tubules to eliminate them from the body for the purpose of controlling the blood hydrogen ion concentration. The hydrogen ions can be secreted against a concentration gradient of about 900 fold.

At many other points in the body, hydrogen ions are transported by secondary active transport, but in these instances, they usually are transported against far less concentration gradients, such as 4 to 1 up to 10 to 1.

(Ref. Guyton & Hall- 11th Edition; Page-54)

Secondary active transport

In secondary active transport, the energy is derived secondarily from energy that has been stored in the form of ionic concentration differences between the two sides of a membrane, created in the first place by primary active transport. Transport depends on carrier proteins that penetrate through the membrane.

Two types :

1. Co-transport
2. Counter transport.

(Ref. Guyton 10th Edition; Page-49)

Co-transport :

When sodium ions are transported out of cells by primary active transport, a large concentration gradient of sodium usually develops very high concentration outside the cell and very low concentration inside. This gradient represents a storehouse of energy because the excess sodium outside the cell membrane is always attempting to diffuse to the interior. Under the appropriate conditions, this diffusion energy of sodium can literally pull other substances along with the sodium through the cell membrane. This phenomenon is called co-transport; it is one form of secondary active transport.

For sodium to pull another substance along with it, a coupling mechanism is required. This is achieved by means of still another carrier protein in the cell membrane. The carrier in this instance serves as an attachment point for both the sodium ion and the substance to be co-transported. Once they both are attached, a conformational change occurs in the carrier protein, and the energy gradient of the sodium ion causes both the sodium ion and the other substance to be transported together to the interior of the cell.

(Ref. Guyton & Hall- 11th Edition; Page-54)

Co-Transport of Glucose and Amino Acids along with Sodium

Glucose and many amino acids are transported into most cells against large concentration gradients; the mechanism of this is entirely by the co-transport mechanism. The transport carrier protein has two binding sites on its exterior side, one for sodium and one for glucose. Also, the concentration of sodium ions is very high on the outside and very low inside, which provides the energy for the transport. A special property of the transport protein is that the conformational change to allow sodium movement to the interior will not occur until a glucose molecule also attaches. But when they are both attached, the conformational change takes place automatically, and both the sodium and the glucose are transported to the inside of the cell at the same time. Hence, this is a sodium-glucose co-transport mechanism.

Sodium co-transport of the amino acids occurs in the same manner as for glucose, except that it uses a different set of transport proteins. Five amino acid transport proteins have been identified, each of which is responsible for transporting one subset of amino acids with specific molecular characteristics.

Sodium co-transport of glucose and amino acids occurs especially in the epithelial cells of the intestinal tract and renal tubules to aid in the absorption of these substances into the blood.

(Ref. Guyton & Hall- 11th Edition; Page-54)

Other important co-transport mechanisms in at least some cells include co-transport of chloride ions, iodine ions, iron ions, and urate ions.

(Ref. Guyton & Hall- 11th Edition; Page-54)

Counter Transport

In counter-transport, sodium ions again attempt to diffuse to the interior of the cell because of their large concentration gradient. However, this time, the substance to be transported is on the inside of the cell and must be transported to the outside. Therefore, the sodium ion binds to the carrier protein where it projects through the exterior surface of the membrane, whereas the substance to be counter-transported binds to the interior projection of the carrier protein. Once both have bound, a conformational change occurs again, with the energy of the sodium ion moving to the interior causing the other substance to move to the exterior.

(Ref. Guyton & Hall-11th Edition; Page-54)

Sodium Counter-Transport of Calcium and Hydrogen ions :

Two especially important counter-transport mechanisms are

sodium-calcium counter-transport and sodium-hydrogen counter-transport. Calcium counter-transport occurs in all or almost all cell membranes, with sodium ions moving the interior and calcium ions, to the exterior, both bound to the same transport protein in a counter-transport mode. This is in addition to primary active transport of calcium that occurs in some cells.

Sodium-hydrogen counter-transport occurs in several tissues. An especially important example is in the proximal tubules of the kidneys, where sodium ions move from the lumen of the tubule to the interior of the tubular cells, whereas hydrogen ions are counter transported into the lumen. This mechanism is not nearly so powerful for concentrating hydrogen ions as is the primary active transport of hydrogen that occurs in some of the more distal renal tubules, but it can transport such large numbers of hydrogen ions that it is nevertheless a key to hydrogen ion control in the body fluids.

(Ref. Guyton & Hall- 11th Edition; Page-55)

Other important Counter-Transport Mechanism :Other counter-transport mechanisms include cation exchane of calcium or sodium ions on one side of the membrane for magnesium or potassium ions on the other side and anion exchanges of chloride ions moving in one direction for bicarbonate ions or sulfate ions moving in the other direcion.

(Ref. Guyton 10th Edition; Page-47,49)

Passive transport

The movement of substance across the cell membrane along the concentration gradient is called passive transport.

The gradients are-

i. Osmotic pressure
ii. Hydrostatic pressre
iii. Gradient of concentration and potential.

Tyses :

i. Diffusion.
ii. Osmosis.
iii Filtration.
iv. Flow due to gravity.

Difference between the active & passive transport

Active	*Passive*
1. Movement occurs against concentration gradient.	1. Movement occurs towards concentration gradient
2. Energy is required.	2. Energy is not required.
3. It depends upon the availability of enzyme and carrier.	3. It depends upon concentration gradient, hydrostatic pressure and osmotic pressure.
4. Membrane always necessary.	4. Membrane may or may not present.

Filtration

It is the process by which undissolved particles are separated from a liquid through a membrane as a result of mechanical force (filtering force).

Filtering force :

i. Gravity.
ii. Hydrostatic pressure.

Filtering membrane :

i. Cloth
ii. Filter paper
iii. Membrane

Filtration depends on :

i. Pressure difference across the filtering membrane.
ii. Pore size of the membrane
iii. Osmotic pressure of the fluid to be filtered

Improtance :

i. Absorption from the small intestine.
ii. Passage of water, salts, food stuff etc. from the blood stream to the tissue fluid.
iii. Formation of urine
iv. Formation of CSF.

Ultrafiltration

It is the process by which small crystalloid molecules are separated through a filtering membrane is called ultrafiltration. Such filtration takes place in the separation of plasma proteins from other plasma solutes in the formation of urine.

Dialysis

Definition : The process by which the more diffusible materials (crystaloid) can be separated from non-diffusible materials (colloid), called dialysis.

Importance of dialysis : Dialysis plays an important role in-

i. Absorption of food stuff from GIT : During absorption from the intestine bigger food particles are held back.
ii. Fluid exchange between blood capillaries and interstitial space : When blood passes through the capillaries the bigger particles albumin, globulin etc. are not allowed to pass into the tissue fluid and are held back into the blood.
iii. In addition, waste products of metabolism accumulates in the body in "renal failure"; dialysis of blood is done through the artificial kidney to remove these waste products clinically.

Surface Tension

Definition : It is the tension which develops on the free surface of the liquid and gases. It is due to the inter-attracting forces in between atoms or molecules.

Importance of Surface tension :

i. The globular shape of an oil drop in water and fat particles in the milk is due to surface tension.
ii. Bile salts reduce the surface tension of fat converting into an emulsion.
iii. The formation of cell membrane is partly due to surface tension of cell cytoplasm.

Substance decreases the surface tension :

i. Bile salts
ii. Ammonia

iii. Organic substances
iv. Strong mineral acids.

Substance increases the surface tension : Inorganic salts generally raise the surface tension.

Interfacial tension

It may be defined as the surface tension exist at the surface of contact (interface) between two immiscible liquids and between a solid and a liquid.

Absorption

It is the process by which the substances enter into the cell, called absorption.

It depends upon -

i. Carrier
ii. Surface area of absorbing membrane.

Adsorption

It is the process by which the substances tends to the surface of the cell not into the cell.

Adsorbate : Any substance that adsorbed is called adsorbate.

Adsorbent : A substance that adsorbs is called adsorbent.

Adsorption occurs due to -

i. Surface tension
ii. Residual valency
iii. Electrical state.

Importance of adsorption.

i. Enzyme action.
ii. Transport of substance in blood
iii. The combination between toxin and anti-toxin, by which they neutralized each other - is an adsorption phenomenon.

***Difference between the* adsorption & absorption.**

Adsorption	*Absorption*
1. It is a peculiar form of combination in which substance adhere together on their surface.	1. It is a process of penitration across the membrane.
2. It is reversible.	2. It is not reversible.
3. No chemical reaction occurs.	3. Chemical reaction occurs.

Isotopes

Definition : The elements having the same atomic number but different atomic weight is called isotopes.

Example : H_2O, D_2O etc.

It depends upon the number of neutron.

Hydrogen have two isotopes :

i. Duterium.
ii. Tritium.

Hydrogen, duterium and tritium having same atomic number 1, but having different atomic weight respectively as 1, 2 and 3.

Classification of isotopes :

Isotopes are of two types :

1. *Natural Isotopes :* The isotopes which remain as mixture in the all natural sources and can be isolated by careful fractionation. Example : H_2O, D_2O.
2. *Radio active Isotopes :* The isotopes which break down constantly into more stable atoms. Ex. Uranium, radi-um etc. It can be prepared artificially by bombardment with a cyclotron or by uranium pile.

Atomic weight

It is the number of weight bearing particles (proton & neutron) present in the atom.

Atomic Number

It is the number of proton present in the atom.

Weight bearing particles : Proton & neutorn.

Weight loss particles : Electrone.

Physiological importance of isotopes

A. *By dilution of radioactivity added :*
   i. Measurement of red cell volume with ^{51}Cr lebelled red blood corpuscles.
   ii. Determination of plasma volume with ^{131}I lebelled serum albumin.
   iii. Determination of total body water with ^{131}I.

B. *Study based on distribution of particular isotopes :*
   i. Uptake of ^{131}I by thyroid gland in thyroid function test.
   ii. Uptake of ^{32}P by malignant tissue in its tracing in the body.

C. *As a radiation source in medicine.*
   i. ^{131}I in the treatment of hyperthyroidism and thyroid cancer.
   ii. ^{32}P in the treatment of leukaemia & polycythemia vera.

Atom

It is the finnest particle of an element which does not posses all the properties but take part in chemical reaction.

Molecule

It is the finnest particle of an element or compound which posseses all the properties but can not take part in chemical reaction.

Isober : The elements having the same atomic weight but different atomic number is called Isober.

Valency : The combining power of one atom of an element (or a radicale), that of the hydrogen atom being the unit of comparison.

Half life

The half life of a radioactive isotope is the time taken by the radiation to come down to half the original strength.

The stability of a radio-active isotope is measured by its half life.

Difference bewtween atom & molecule

Atom	*Molecule*
1. Smallest particle of an element.	1. Smallest particle of an element or compound.
2. Cna not exist in the free state.	2. Can exist in free state.
3. Can take part in chemical reaction.	3. Can not take part in chemical reaction.

Isomer & Isomerism

Isomer

Definition : It is the state of compounds having same number of atoms but different atomical arrangement.

Isomerism : It is the phenomenon where different chemical compounds having same molecular formula but differ in the atomic arrangement of the molecule.

Types of Isomer :

a. *Sterio-isomer* : Compounds which are identical in composition and differ only in spatial configuration are called sterio-isomers.

Two such isomers of glucose; one of which is the mirror immage of other are : L-Glucose and D-Glucose.

b. *Optical isomerm* : It is a phenomenon where isomers show different optical activities i.e. rotating the plain of polarised light beam due to presence of asymmetric carbon atoms.

i. *Dextro-rotatory :* A compound which causes rotation of polarised light to right or clock-wise is called dextro-isomers or dextro-rotatory.

ii. *Levo-rotatory :* A compound which causes rotation of polarized light to left or anti-clock wise is called levo-isomer or levo-rotatory.

c. *Epimer* : When isomerism occurs around a single carbon atom then it is called epimer.

Example : Galactose and glucose are epimer to each other.

Asymmetric atom

A atom to which four different atom or groups of atoms are attached is called asymmetric atom.

Example : Glyceraldehyde.

Specific rotation

A constant rotation is called specific rotation.

Mutarotation

Muta means change and *rotation* means rotated form , So change in specific rotation is called mutarotation.

When an aldohexose is first dissolved in water, its optical rotation gradually changes until a constant rotation characteristic of sugar is reached due to changes of alpha to beta form and vice versa. This phenomenon is known as mutarotation.

Carbohydrate

Definition: Carbohyrates are polyhydric alcohol having aldehydes or keton groups or compounds which yeilds those derivatives on hydrolysis. Here hydrated carbon is present.
Example : Glucose, Fructose, Starch etc.

Sources of carbohydrate
Carbohydrates are widely distributed in nature. There are three main sources-

1. *Sugars* : Mono & Disaccharides- Glucose, fructose, galactose, sucrose, lactose etc.
2. *Starch* : Present in cereals, roots, tuber, plant stems etc.
3. *Cellulose* : Vegetable, cereals, fibrous lining of fruits.

Classification
Classified into four major groups according to the number of simple sugar unit present in the molecule. Such as -

A. ***Monosaccharides (simple sugar)*** : Those carbohydrates which can not be hydrolysed further into a simpler form. They contain only one unit of simple sugar.
Example : Glucose, Fructose etc.

Monosaccharides are subdivided into-

1. Trioses, tetroses, penoses, hexoses or heptoses according to the number of carbon atom present in the molecule.
2. Aldoses and ketoses, according to the nature of reducing group (aldehyde or ketone group) they contain.

Classification of monosaccharides

	Aldoses	*Ketoses*
a. Trioses	Glycerose	Dihydroxyacetone
b. Tetroses	Erythrose	Erythrulose
c. Pentoses	Ribose	Ribulose
d. Hexoses	Glucose	Fructose.

B. ***Disaccharides*** : Those which yield two molecules of same or different monosaccharides when hydrolysed.

Example : *Sucrose* (Glucose + Fructose), *Maltose* (Glucose + Glucose), *Lactose* (Glucose + Galactose).

Types :
1. Reducing : Maltose, Lactose.
2. Non-reducing : Sucrose.

C. ***Oligosaccharides*** : Those which yield 3-10 monosaccharide units on hydrolysis.

Example : Rabinose, Raffinose etc.

D. ***Polysaccharides*** :
Those which yield an indefinetely larger number (more than 10 melecules) of monosaccharides on hydrolysis.

Example : Starches, dextrins, glycogen etc.

Classification of polysaccharide :
1. *According to the nature of constituents*
   a. *Pentosans :* Those, made up of pentose units.
   Example : Inulin etc.
   b. *Hexosans :* Those, made up of hexose units .
   Example : Starch, dextrin etc.
2. *According to the nature of content-*
   a. *Homopolysaccharides :* When they are made up of same kinds of monosaccharides.
   Example : Starch, dextrin, cellulose, glycogen etc.
   b. *Heteropolysaccharides :* When they are made up of two or more kinds of monosaccha-rides or their derivatives.
   Example : Heparin, hyaluronic acid, chondroitin sulphate etc.

Difference between aldose and ketose :

Aldose	*Ketose*
1. Aldose derived from primary alcohol.	1. Ketose derived from secondary alcohol.
2. Aldose contains aldehyde group.	2. Ketose contains Ketone group.

Sugar Unit :
The sugar containing 3-7 carbon atom is called sugar unit.

Starch
1. *Definition* : It is the most important food source of carbohydrate and is found in cereals, potatoes, legumes and others.
2. Structure : It is formed of a α-glucosidic chain. This produces only glucose on hydrolysis. So, it is called glucosan.
   It has 2 parts :
   i. Amylose (15-20%) : non branched hellical structure.
   ii. Amylopectin (80-90%) : consists of branched chains composed of 24-30 glucose residues united by 1→ 4 linkages in the chains and by 1→ 6 linkages at the branch points.

Glycogen
1. *Definition* : It is the storage form of poly saccharide in animal body.
2. *Structure* : It has a branched structure with straight chains of 11-18-α-D-glucopyranose residues with branching by means of a (1→ 4) glucosidic linkage.

Cellulose
1. Definition : It is the main carbohydrate component of plant.
2. Structure : It consists of β-D-glucopyranose units linked by β (1→ 4) bonds to form long, straight chains strengthened by cross linked hydrogen bonds. It is not digested by human body due to absence of hydrolase which break down β linkage.

3. Importance : It is an important source of bulk in the diet, thereby stimulating peristalsis and elimination of stool.

Glycosides

Glycosides are compounds formed from a condensation between a monosaccharide, or monosaccharide residue and the hydroxyl group of a second compound that may or may not (incase of glycone) be another monosac charide.

Example : cardiac glycoside.

Deoxy sugar : Are those in which a hydroxyl group attached to the ring structure has been replaced by a hydrogen atom.

Example : Deoxyribose.

Amino sugar : Sugars containing an amino group are called amino sugars.

Example : D-glucosamine, D-Galactosamine, and D-mannosamine etc.

(Ref. Herper's)

Q. ***Which one is the most important in monosaccharide and polysaccharide?***

a. *In Monosaccharide :* Hexoses are the most important class of monosaccharides. They are widely distributed in nature either in free form or in combination with other molecules. Biologically important hexoes are glucose fructose, galactose and manose, among them glucose is most important.

b. *In polysaccharide :* Glycogen is the most important plysaccharide for the human being because via the pathway of glycogenolysis it liberate glucose units for ready energy.

Important dietary carbohydrate :

1. Monosaccharides : Glucose, fructose
2. Disaccharides : Maltose, sucrose, lactose
3. Polysaccharides : Starch, glycogen, cellulose.

Properties of carbohydrate

1. They are colourless crystaline compounds having a sweet taste.
2. Chemically they are derivatives of polyhydric alcohols. The aldoses are derived from primary alcohols and ketoses from secondary alcohols.
3. *Formation of ester :* By virtue of alcohol group they easily form esters with acids.
4. *Reducing power :* By virtue of the aldehyde or ketone groups, the simple sugars are powerful reducing agent.
5. *Isomerism :* Due to the presence of asymmetric carbon atoms in the molecule, monosaccharides may remain in many isomeric forms.
6. *Optical rotation :* Simple sugars rotates in the plane of polarised light and therefore may exists in either dextro or levo forms.
7. *Condensation :* Simple sugars condense and form bigger carbohydrate molecules e.g polysaccharides.
8. *Osazone formation :* All reducing sugars condense with phenylhydrazine and produce osazone compounds.
9. *Reduction :* The monosaccharides may be reduced to their corresponding alcohols by reducing agents such as sodium amalgam.
10. *Ring structures of sugars :* Sugars not only remain as straight chain compounds but may also remain in the form of rings.
11. Fermentation by yeast and other micro-organisms.

Functional (biomedical) importance of carbohydrate

i. Ready source of energy : 4.1 Kcal/gm of carbohydrate.
ii. It also constitutes the structural material of the organism.
iii. Acts as important storage of food material of the body i. glycogen.
iv. Actively concerned with protein and fat metabolism i.e protein and fat metabolized on the back ground of carbohydrate.
v. Highly specific function :
   a. Ribose : major constituents of nucleic acids
   b. Lactose : sugar of milk
   c. Fructose : give energy to sperm.
vi. It gives nutrition to the nervous tissue & retina.
vii. It prevents ketosis.
viii. Carbohydrate is a protein sparer, that is carbohydrate is burned in preference to the burning of protein.
ix. Antibodies, clotting factors & peptide hormones contain oligosaccharides.
x. Diseases associated with carbohydrate are- diabetes mellitus, galactosaemia, glycogen storage diseases and lactose intolerance.
xi. Sugar solution is used as I.V fluid.
xii. Some drugs are chemically glycosides- are used as drug i.e cardiac glycosides, streptomycin.

L and D series of the sugars

The orientation of the H and OH group around the carbon atom just adjecent to the terminal primary alcohol (e.g. carbon atom 5 in glucose) determines the family to which the sugar belongs. When the "OH" group on this carbon is on the right, the sugar is the member of D-series, when it is on the left, it is a member of L-series.

Q. ***Why sucrose is a non reducing sugar?***

Ans. Sucrose contains glucose and fructose which are linked together through their reducing groups and as a result of this, no reducing group is free and hence it does not respond the test. So sucrose is non reducing.

Glucosan : Glucosan are those which yield only glucose on hydrolysis.

Example : Startch, Glycogen. Dextrin etc.

Fructosan : Fructosan are those which yield only fructose on hydrolysis.

Example : Inulin.

Inversion of sucrose : Inversion of sucrose reffers to that

phenomenon when the dextrorotatory property of sucrose solution changes into levorotatory form because of the hydrolysis of sugar into glucose and fructose.

Sucrose is an invert sugar - Explain?

Sucrose is dextrorotatory but on hydrolysis it yields a crude mixture (Glucose + Fructose) which is often called invert sugar because the strongly levorotatory fructose inverts the previous dextrorotatory action of sucrose. So sucrose is called invert sugar.

Reducing sugars

Are those which posses free aldehyde or ketone group called reducing sugar.

Example : All monosaccharides, maltose, lactose etc.

Properties of monosaccharide

1. These are white (colourless) crystaline compound having sweet taste.
2. Condensation into polysaccharide.
3. They have reducing property due to presence of aldehyde or ketone groups.
4. They can produce esters due to presence of alcohol groups.
5. Properties not dependent on alcohol or aldehyde or ketone groups-
   a. Formation of alcohol.
   b. Formation of osazone sugar.
   c. Formation of glycosides.
   d. Optical rotation and isomerism.
   e. Fermentation by yeast or bacteria.
   f. Formation of amino sugar.
   g. Acetylation.
   h. Oxidation.

Glucose

Properties :

i. Glucose or grap sugar is the most important of the monosaccharides because of its utility. It is sometimes called dextrose due to its dextrorotatory property.

ii. Glucose is present in the body as glucose phosphate, in milk sugar as lactose (glucose & galactose), in combination with proteins as glycoproteins, glucosamine.

iii. Some polysaccharides such as glycogen (liver and muscle), starch (plant), dextrin and cellulose (supporting structure of plant), yield glucose on hydrolysis.

iv. When it is completely burn to CO_2 and H_2O energy is evolved.

v. Structure of glucose: Glucose may be present in two forms-
   a. A straight chain compound (L & D form).
   b. A cyclic compound (a & b form).

Dis-similarities between glucose and fructose

Glucose	*Fructose.*
1. Aldose.	1. Ketose.
2. Functional group lst carbon atom.	2. Functional group 2nd carbon atom.
3. Seliwanoff test (-ve) negative.	3. Seliwanoff test (+ve) positive.

Enediol :

t is the active form of that sugar when treated with alkali, it acts as a strong reducing agent. It is formed by enolization process.

Lipids

Definition : Are ester like compounds of fatty acids which are insoluble in water but soluble in fat solvents, e.g. chloroform, ether, benzene etc.

Properties of lipid :

A. ***Physical :***

1. *Solubility :* They are insoluble in water but readily soluble in fat solvents i.e ether, chloroform, benzene etc.
2. They are tasteless, odorless, colourless and neutral in reaction.
3. *Melting point :* Different fats have different melting points. Thus beef fat melts at 49.5°C, human fats melts at about 17°C.
4. *Specific gravity :* It is less than 1 i.e lighter than water.
5. Neutral fats are non volatile and may be crystalized.
6. *Spreading and surface tension :* When a liquid fat is poured on water, it spreads uniformly over the surface of water and reduces the surface tension of water.

B. ***Chemical :***

1. *Hydrolysis :* By boiling with acids or alkalis or by applying superheated steam fats can be completely hydrolysed into fatty acids and glycerol.
2. *Rancidity :* Rancidity is a chemical changes that results in unpleasant odors and tastes in a fat. This is due to partial hydrolysis causing liberation of volatile fatty acids e.g Butyric acid from butter.
3. *Hydrogenation:* Unsaturated fatty acids are usually liquid at room temperature and commonly called oils. These oils can take hydrogen at their double bond in presence of catalyst (nickle) and converted into solid fats. This process is called hydrogenation or hardening of fats.
4. *Oxidation :* Unsaturated fatty acids when react with oxygen to form a number of substances including aldehydes and ketones which may react further to form complex resinous compound.

Classification of lipid

Lipids are classified into -

A. *Simple lipid* : Esters of fatty acids with various alcohols.
   i. *Neutral fats :* Esters of fatty acids with glycerol e.g oil, triglyceride.
   ii. *Waxes :* Esters of fatty acids with higher alcohols other than glycerol e.g cholesterol ester, vitamin D ester.

B. *Compound lipids* : Esters of fatty acids with alcohols and containing other groups e.g PH_4, sugar, protein, nitrogenous substances etc.
   Example : Phospholipids, glycolipids, sulpholipid, lipoprotein etc.

C. *Derieved lipid* : Substances derieved from hydrolysis of simple lipid and compound lipid are called derieved lipid. e.g, saturated and unsaturated fatty acids, steroids etc.
   i. ***Fatty acids*** :
      a. Saturated fatty acid : Having no double bond e.g stearic acid, palmitic acid
      b. Unsaturated fatty acid
         1. Monounsaturated fatty acid e.g oleic acid
         2. Polyunsaturated fatty acid (Ecosanoids- having 20 carbon atoms)
            * Protanoids : Protaglandin, protacyclins, thromboxanes
            * Leukotriens & lipoxins
   ii. ***Steriods*** :
      a. Hormones : Glucocorticoids, mineralo-corticoids, cortical sex hormones
      b. Steriods : Cholesterol
      c. Bile acids.

Biological importance of lipid

i. Lipids are the most concentrated source of energy. Their calorie value is 9.3 kcal/gm.
ii. Lipids provide essential fatty acids.
iii. Lipid acts as reserved food materials.
iv. Lipid is a structural component of the cell membrane.
v. Lipid acts as a insulating material.
vi. Lipid protects the internal organ. e.g kidney etc.

Fat

Are the esters of fatty acid with glycerol. It is solid at ordinary temperature.

Oil

Unsaturated fatty acids are usually liquid at room temperature and commonly called oils.

Difference between fats and lipids :

Fats	*Lipids*
1. Fats are esters of fatty acids with glycerol.	1. Lipids are ester like com pound of fatty acids.
2. Trihydric alcohol present.	2. Alcohol present is more than trihydric.
3 It contains short chain (upto 10-12 c) of fatty acids.	3. It contain long chain (more than 12 c) of fatty acid.

Iodine number

Means the number of grams of iodine absorbed by 100 gm of fat.

Importance : It indicates the degree of unsaturation in the fat. Higher the iodine number the more will be the degree of unsaturation.

Saponification : Hydrolysis of fat by an alkali is called saponification.

Saponification number : Means the amount of KOH in mg require to saponify completely 1 gm of fat.

Importance : It gives an idea, about average chain length of the fatty acids present in the fat.

Alkali hydrolysis :

The process of saponification is called alkali hydrolysis.

Soap :

After saponification glycerol is released and fatty acid will produce salts with alkalis. These salts are known as soap.

Acid number :

It may be defined as mg of KOH required to neutralize the free fatty acid present in 1 gm of fat.

Fatty acid

Definition : Fatty acids are obtained from hydrolysis of fats.

Classification :

A. *On the basis of saturation :* Pl see above

B. *On the basis of carbon atom :*
   1. *Long chain fatty acids :* Fatty acids containing more than 10 carbon atoms.
   2. *Short chain fatty acids :* fatty acid containing less than 10 carbon atoms.

Fatty acids of physiological importance :

1. *Palmatic acid* : 16 Carbon atom (Saturated)
2. *Stearic acid* : 18 Carbon atom (Saturated)
3. *Oleic acid* : 18 Carbon atom (Unsaturated).

Essential fatty acids

Essential fatty acids are those which cannot be synthesized in our body hence are supplied in the diet.

Example :

i. Linoleic acid
ii. Linolenic acid
ii. Arachidonic acid.

Properties :

1. Essential faty acid of vegetable oils have low melting point & iodine number.
2. They become saturated fatty acids on hydrogenation and the oils bbbecomes solid fats.

Importance :

i. Essential fatty acids reduces the plasma cholesterol concentration, thus it can reduce the coronary artery diseases.
ii. Precursor of eicosanoids (prostaglandin, thromboxane, leukotrienes)
iii. For synthesis of structural lipid.
iv. Concerned with optimum gonadal activity and it is directly related to sterility.
v. The deficience of essential fatty acid in the diet of baby cause eczema.

Q. *Why essential fatty acids are called so?*

Ans. They play great role in proper functioning of many metabolic processes and are not synthesized in the body in quantities sufficient to meet the daily requirement, there fore it must be supplied in diet. So it is called essential fatty acids.

Steroids : Substances possessing cyclopentanoperhydrophenanthrene nucleus are called steroids.

Phospholipid

1. *Definition* : Phospholipids are composed of fatty acids, glycerol, phosphoric acid and in most cases a nitrogenous base.
2. *Example* :
   a. Phosphatidyl inositol
   b. Phosphatidylglycerls
   c. Phosphatidyl serine
   d. Phosphatic acid
   e. Phosphatidylethanolamine
   f. Sphingomyelins
   g. Lysophospholipids
   h. Plasmalogen.
3. *Distribution* : Widely present in the-
   a. Nervous tissue
   b. Brain
   c. Liver
   d. Kidney
   e. Pancrease
   f. Heart etc.
4. *Importance* :
   a. Takes part in the synthesis of biological membranes
   b. Helps in blood coagulation
   c. In bile, it keeps the cholesterol in solution
   d. In the form of surfactant, it help in expansion of lung
   e. Act as a second messenger of different hormones
   f. Phospholipids of myelin sheath provides insulation.

Lipoprotein

1. *Definition* : Lipoproteins are conjugated proteins consisting of simple proteins combined with lipid components-triglycerides, cholesterol, and phospholipids.
2. *Classification* :
   a. Chylomicron
   b. Very low density lipoprotein - VLDL
   c. Low density lipoprotein - LDL
   d. High density lipoprotein - HDL
3. Normal blood values :
   a. LDL : <150 mg/dl
   b. HDL : 55 - 65 mg/dl

Clinical importance :

1. LDL : Transport cholesterol from liver to peripheral tissues. It may be responsible for atherosclerosis.

2. HDL : Transport cholesterol from peripheral tissues to liver. It act as a scavanger. Thus it can protect coronary heart disease.
3. VLDL : Transport exogenous triglycerides from liver to peripheral tissues for energy.
4. Chylomicron : Transport exogenous triglycerides from intestine to liver through lymphatic circulation.

Apo-lipoprotein

1. *Definition* : The protein moiety of a lipoprotein is known as an apo-lipoprotein. It is proteins or polypeptides.

   It constitute about 70% of some HDL and 1% of chylomicrons. Some apolipoproteins are integral and cannot be removed, whereas others are free to transfer to other lipoprotein

2. *Types with distribution* :

Apo A_1 and A_2	HDL
Apo B_{48}	Chylomicrons
Apo B_{100}	VLDL, LDL
Apo C_1, C_2, C_3	Not native to any lipoprotein but in almost all lpoproteins
Apo E	Not native to any lipoprotein but in almost all lpoproteins.

3. *Functions of lipoproteins* :
   a. Structural component of lipoprotein
   b. Act as enzyme co-factors e.g apo-C-II for lipoprotein lipase.
   c. Act as a ligands e.g binding and recognition of lipoprotein with corresponding receptors.

Cholesterol

1. *Definition* : It is a complex monohydric alcohol and steroid in nature.
2. *Cholesterol turnover* : 1 gm/day
   a. *Input* : 1 gm/day
      i. Endogenous prroduction : 500 mg/day
      ii. Dietary : 500 mg/day

      Food : Egg, milk, liver, brain, skin etc.
   b. *Output* : 1 mg/day
      i. Bile salt : 500 mg/day
      ii. Faecal neutral steroid : 400 mg/day
      iii. Skin desquamation : 100 mg/day

Importance :

1. Essential constituent of all cells
2. Increase the cell membrane permeability
3. Precuesors of bbile acids, adrenocortical hormones, sex hormones, vitamin D, and cardiac glycosides
4. Increase in plasma cholesterol level (hypercholesterolemia) may cause atherosclerosis.

Lipid profile

Different types of lipids are present in plasma of blood in different amounts. It is knnown as lipid profile.

1. Triglycerides	: <150	mg %
2. Cholesterol	: 150 - 220	mg %
3. HDL	: >40	mg %
4. LDL	: <130	mg %
5. LDL : HDL	: 2.5 : 1	
6. Cholesterol : HDL	: 3.5 : 1	

Prostaglandin

1. *Definition* : Prostaglandins are 20 carbone hydroxy fatty acids containig a five membered ring.
2. *Synthesis* :

   Membrane phospholipids

   Phospholipase

   Arachidonic acid

   Cyclooxygenase

   Prostaglandins
3. *Distribution* :
   a. Lungs
   b. Kidney
   c. Thyroid
   d. Spleen
   e. Brain
   f. Iris
   g. Endometrium etc.
4. *Functions* :
   a. Causes vasodilation → decreases blood pressure
   b. It mediates inflammation
   c. It causes pain sensation
   d. It causes contraction of muscle
   e. It Inhibits gastric secretion
   f. It takes part in spermatogenesis.

Protein

Definition : Protein is complex organic nitrogenous compound composed of amino acids linked together by peptide bonds.

Sources : Meats, fish, milk, egg, pulses and vegetables etc.

Classification

Protein is classified into three groups (broad based types) -

A. *Simple protein :* The protein which gives only amino acid on hydrolysis is called simple protein. These are pure protein and have no nonprotein group in the molecules.
Example : Albumins, globulins etc.

B. *Conjugated protein :* These contains amino acid units with one or more additional nonprotein (prosthetic) group or groups.
Example : DNA, RNA, Hb etc.

C. *Derieved protein :* These proteins are not found in nature as such. They are as products of hydrolysis of the native protein molecules. The gradual stages are as follows:
Protein –> Proteoses ——> Peptones ——> Peptides —> polpeptide.

Polar or salt linkage : When two amino acids join together without forming peptide linkage, they are known to form polar linkage.

On the basis of source :

1. *First class proptein* : Proteins of high biological value which contain all the essential aminoacids.
Source : Animal sources such as meat, fish, egg, milk.
2. *Second class protein* : Protein of low biological value which are poor in essential amino acids.
Source : Plant sources such as vegetables- pulses, cereals, leans, nuts, oil seed etc.

On the basis of biological function :

1.	Catalytic	: enzymes
2.	Contractive	: actin, myosin
3.	Hormonal	: Insulin
4.	Structural	: collagen, elastin
5.	Transport	: albumin, Hb, lipoprotein, transferrin
6.	Regulatory	: calmodulin
7.	Gene regulatory	: histones
8.	Protective	: fibrin.

Zwitterion : At a certain pH the number of positive charge is equal to the number of negative charge and protein remains as zwitterion form.

Denaturation of protein : Means unfolding of the protein molecule.

Chromoproteins :

i. Haemoglobin
ii. Myoglobin
iii. Cytochrome
iv. Catalase.

Properties of protein :

I. *General properties* :

1.	Nature	: Colloidal
2.	Taste	: Generally tasteless
3.	Odour	: Odourless
4.	Molecular weight	: High
5.	Crystalysation	: Globular proteins mostly crystalline.

6. *Solubility* : Different for different proteins. They are generally soluble in water & salt solution and insoluble in fat solvent.
7. *Acidity & alkalinity* : All proteins can behave like acids or bases depending on whether the medium is basic or acidic.
8. *Isoelectric point* : Each protein has a particular isoelectric point (pH) at which it can be precipitated.
9. *Diffusibility* : Most proteins cannot pass through the membranes of the cells.
10. Protein has no melting point
11. Osmotic pressure
12. Viscosity.

II. *Chemical properties* :

1. Proteins are polymers of amino acids.
2. They are composed of C, H, O, N & sometimes S, P.
3. Denaturation: Proteins undergo a change by the application of heat, addition of acid/alkali and some organic solvents. This is called denaturation of protein.
4. Coagulation : Proteins undergo coagulation by heat and strong acid.
5. Precipitation : Proteins undergo precipitation by metalic salt & alkaline reagent.
6. They give colour reaction-
   i. Biuret test
   ii. Millons test
   iii. Xanthoprotein test
7. Hydration.

Biomedical importance of protein :

i. Structural component of cell membranes, organelles & cytoskeletal structures.
ii. Transport of O_2 by Hb or electrone by the cytochromes.
iii. Acts as carrier e.g Na^+-glucose co transporter.
iv. Maintenance of fluid balance by serum albumin.
v. They help in formation of enzymes & many hormones.
vi. The dietary protein regulates the supply of nitrogen & sulphur.
vii. They perform hereditary transmission by nucleoprotein.
viii. They help in blood clotting by prothrombin & fibrinogen.
ix. Some proteins are present as storage e.g ferritin is stored being formed by protein & iron.
x. They help in movement of muscle fibre by actin & myosin.
xi. Source of energy : 4.2 Kcal/gm.

xii. Diseases associated with protein maturation are Dire consequences, Ehlers-Danlos syndrome & scurvy.

Amino Acid

Definition : Amino acids are organic acid in which one or more hydrogen atoms are replaced by amino ($-NH_2$) group. Thus it contains at least a free amino ($-NH_2$) group, and a carboxyl (-COOH) group.

In an α amino acid, both amino and carboxyl groups are attached to the same (α) carbon atom.

Classification of amino acid :

Amino acids are classified into two catagories :

A. *According to their functional group*
   1. *Neutral amino acids* : monoamino-monocarboxylic acid i.e glycin, alanine etc.
      i. *Aliphatic series*
         a. Normal series i.e glycine
         b. Hydroxy series i.e serine
         c. Sulphar containing i.e methionine
      ii. *Aromatic series*
         a. Normal series i.e tryptophan
         b. Hydroxy series i.e tyrosine
   2. *Acidic amino acids* : monoamino dicarboxylic acid i.e aspartic acid, glutamic acid etc.
   3. *Basic amino acids* : diaminomono-carboxylic acid i.e agrinine, lysine etc.
   4. *Imino acids* : containing imino group but no amino group) i.e proline.

B. *Accroding to their biological value* :
   a. Essential amino acids : i.e isoleucine, valine etc.
   a. Semi-essential amino acids : i.e arginine, histidine
   b. Non-essential amino acids : i.e glycine, alanine, asparate, glutamate etc.

Essential amino acid

Essential amino acids are those which can not be synstheized by the body but needed for the growth of the body and, hence they have to be supplied in the diet. There are eight essential amino acids.

Example :
1. Valine
2. Leucine
3. Isoleucine
4. Lysine
5. Threonine
6. Methionine
7. Phenylalanine.
8. Tryptophan

Non essential amino acids

Non essential amino acids are those which are synthesized by the body.

Example :
i. Glycine.
ii. Alanine.
iii. Serine.
iv. Cysteine.
v. Asparagine.
vi. Tyrosine.
vii. Aspartic acid.
viii. Glutamic acid.
ix. Proline
x. Glutamine.

Semiessential amino acids

Those amino acids which are partly synthesized by the body are called semiessential amino acids.

Example : arginine, histidine.

Nucleoprotein

1. *Definition* : Nucleoproteins are conjugate proteins containing neuclic acid as non protein prosthetic group and a base protein like protamines or histones.
2. *Example* :
   i. Nucleoprotamine
   ii. Nucleohistones
3. *Distribution* :
   i. In ribosomes of all living cells
   ii. Virus - consists entirely of nucleoproteins.
4. *Compositions of nucleoproteins* :
   A. Basic proteins (protamines or histones)
   B. Nucleic acid (DNA, RNA)
      i. Phosphoric acid
      ii. Nucleosides
         a. Bases
            1. Purine : adenine, guanine
            2. Pyrimidine : cytosine, thymine (DNA) uracil (RNA)
         b. Sugar :
            1. D-ribose (RNA)
            2. 2-Deoxy D-ribose (DNA).

Nucleic acids

Nucleic acids are high molecular weight polyanionic molecules composed of nucleotides i.e nucleic acids are polynucleotides

Types : It is two types -
i. Deoxyribose nucleic acid - DNA
ii. Ribose nucleic acid - RAN.

Component of nucleic acid :

Nucleic acid :
   i. Phosphoric acid
   ii. Nucleosides
      a. Bases

1. Purine
   Major :
   * Adenine
   * Guanine
   Intermediate :
   * Xanthhine
   * Hypoxanthine

2. Pyrimidine
   * Cytosine
   * Thymine (DNA)
   * Uracil (RNA)

b. Sugar
D-ribose (RNA)
2-Deoxy D-ribose (DNA).

Nitrogenous base

Nitrogenous bases are of two types -

i. *Purine base* : Adenine and guanine both are present in DNA & RNA.

ii. *Pyrimidine base* : Cytosine and uracil are present in RNA. Where as cytosine along with thiamine are present in DNA.

Nucleotides

Nucleotides are the monomer units or building blocks of nucleic acids - serve multiple additional functions. They form a part of many coenzymes and serve as donors of phosphoryl groups (i.e ATP or GTP), of sugars (i.e UDP- or GDP sugars), or of lipid (i.e CDP-acylglycerol).

These are the structural unit of nucleic acid containing a *purine or pyrimidine* base attached to a sugar- *ribose or deoxyribose* by a a glycosidic linkage and combined with *phosphoric acid.*

Example :

Nucleotide	*Base*	*Nucleosides*
1. Adenosine monophosphate- AMP	Adenine	Adenosine
2. Guanosine monophosphate- GMP	Guanine	Guanosine
3. Uridine monophosphate- UMP	Uracil	Uridine
4. Cytidine monophosphate- CMP	Cytosine	Cytidine
5. Thymidine monophosphate-TMP	Thymine	Thymidine

(Ref. Harper's Illustrated Biochemistry 26th ed, Page-286,288)

Importance of nucleotides :

1. They are the building block or monomer of nucleic acids
2. They can act as a co-enzymes i.e NAD, FAD, FMN
3. They can act as intracellular second messenger i.e cAMP, cGMP etc.
4. They can store and transfer energy.
5. They participate in synthetic process of different bio-molecules i.e UDP- in glycogen synthesis
6. They participate in different phosphorylation process.

Nucleosides

Sugar-base combination is called nucleosides. A nucleosides is composed of a purine or a pyrimidine base to which a sugar (D-ribose or 2-deoxy D-robose) is attached in β-linkage at N_9 or N_1 respectively.

Example with composition :

a. *Nucleosides containing Purine bases*	*Base*	*Sugar*
1. Adenosine	Adenine	D-ribose
2. Deoxy adenosine	Adenine	2-Deoxy ribose
3. Guanosine	Guanine	D-ribose
4. Deoxy guanosine	Guanine	2-Deoxy ribose
b. *Nucleosides containing Pyrimidine bases :*	*Base*	*Sugar*
1. Uridine	Uracil	D-ribose
2. Cytidine	Cytosine	D-ribose
4. Deoxy cytidine	Cytosine	2-Deoxy ribose
5. Deoxy thymidine	Thymine	2-Deoxy ribose

Lipoprotein *(Described in lipid section)*

DNA

It is a complex protein of high molecular weight consisting of deoxyribose, phosphoric acid, and four bases (2 purines and 2 pyrimidines). DNA is found mainly in the chromosomes of the cell nucleus.

Components of DNA :

i. Sugar : 2-deoxy-D-ribose
ii. Acid moiety : Phosphoric acid
iii. Bases :
   a. Purines : Adenine & Guanine
   b. Pyrimidines : Cytosine & Thymine

Function of DNA :

The genetic information store in the nucleotide sequence of DNA serves two purposes-

i. It is the source of information for the synthesis of all protein molecules of the cell & organism.
ii. It provides the information inherited by daughter cells or offspring.

(Ref. Guyton 11th Edition)

RNA

RNA (Ribonucleic acid) is a polymer of purine & pyrimidine ribonucleotides linked together by 3, 5, - phosphodiaster bridge. RNA is found mainly in the cytoplasm & nucleolus.

Components of RNA :

i. Sugar : D-ribose
ii. Acid moiety : Phosphoric acid
iii. Bases :
   a. Purines : Adenine & Guanine
   b. Pyrimidines : Cytosine & uracil

Types of RNA :

1. *Messenger RNA (m RNA) :* Which carries the genetic code to the cytoplasm for controlling the formation of the proteins.
2. *Transfer RNA (t RNA) :* Which transports activated amino acids to the ribosomes to be used in assembling the protein molecules.
3. *Ribosomal RNA (r RNA) :* Which along with about 75 different proteins, forms the ribosomes, the physical and chemical structure on which protein molecules are actually assembled.

Functions of RNA : It is involved in protein synthesis.

(Ref. Guyton 11th Edition; Page 31)

Transcription

Assembly of the RNA molecule from activated nucleotides using the DNA strand as a template- the process is called transcription.

(Ref. Guyton & Hall-11th edition; Page-33)

Assembly of the RNA molecule is accomplished by DNA under the influence of the enzyme RNA polymerase.

Translation

The process of formation of proteins on the ribosomes is called translation.

(Ref. Guyton& Hall-1th Edition; page-33)

Trait	*DNA*	*RNA*
1. Bases	1. Adenine, guanine, cytosine and thymine.	1. Adenine, guanine, cytosine and uracil.
2. Sugar moiety	2. Deoxyribose.	2. D-ribose
3. Structure	3. Have 2 strands of antiparallel double helical molecule.	3. Single-stranded molecules.
4. Situation	4. Solely intranuclear and mitrochondrial.	4. Both extra & intranuclear (cytoplasm & nucleolus).
5. Functions	5. i. Carry genetic information from one generation of cells to the next & undergo mutation.	5. i. Carry no genetic information & undergo no mutation.
	ii. Concerned with source of information protein synthesis.	ii. Concerned with protein synthesis.

5
Blood System

Definition : Blood is a ***specialised fluid connective tissue*** in which there is liquid intercellular substance (plasma) and formed elements -(RBC, WBC and platelets) suspended in the plasma which circulates in closed system of blood vessels. It is red, thick and slightly alkaline.

Composition of blood

Blood is composed of-

A. ***Cellular substances :*** 45% (42-45%)
   i. Erythrocytes or red blood corpuscles (RBC)
   ii. Leukocytes or white blood corpuscles (WBC)
   iii. Platelets or thrombocytes

B. ***Liquid intercellular substances :*** i.e, plasma - 55% (55 - 58%) :

   Plasma contains -
   i. *Liquid :* (91 - 92 %) - water
   ii. *Solids :* (8 - 9%) :
      a. *Inorganic constituents (0.9%)* : Sodium, potassium, calcium, magnesium, phos-phorus, iron, copper etc.
      b. *Organic constituents :*
         i. *Proteins - 7.5% :* serum albumin, serum globulin, fibrinogen, prothrombin, etc.
         ii. *Non-Protein nitrogenous substances (NPN) :* Urea, uric acid, xanthine, hypoxanthine, creatine, creatinine ammonia, amino acids etc.
         iii. *Fats :* Neutral fat, phospholipid, choles-terol, cholesterides etc.
         iv. *Carbohydrates :* Glucose, sucrose, etc.
         v. *Other substances :* Internal secretions, anti-bodies and various enzymes (amylases, proteases, lipases, phospha-tases, etc.)
         vi. *Colouring matters :* Yellow colours of plasma is due to small amount of bilirubin, carotine and xanthophyllin.

Properties of blood

i.	Blood volume	: 5 - 6 litres
ii.	Normal reaction	: Slightly alkaline, pH = 7.36 - 7.45
iii.	Specific gravity	: 1.052 - 1.060
iv.	Viscosity	: 4.5 times more viscus than water.
v.	Temperature	: 36-38°C
vi.	Osmotic pressure	: Average 25 mm of Hg.
vii.	Taste	: Salty.

viii. Colour : Red, due to presence of haemoglobin inside RBC.

Viscosity of blood

Viscosity of blood is the ratio of time of flow of a given volume of blood with same volume of distilled water, while passing through a specially prepared tube known as viscometer. It is about 4.5 times more viscus than water.

The ratio of relative viscosities of water, plasma and whole blood is roughly- 1 : 1.8 : 4.5 respectively.

It depends upon :
i. The amount of plasma protein
ii. Number and volume of cellular elements.
iii. CO_2 tension
iv. Temperature.

Viscosity rises for following causes :
i. Acidosis
ii. Hyper calcaemia
iii. Hyper glycaemia
iv. Polycythemia
v. Cyanosis
vi. Diabetes mellitus

Viscosity is reduced in :
i. Anaemia
ii. Fever
iii. Exercise
iv. Oedema
v. Lymphatic leukaemia
vi. Malaria
vii. Rise of temperature.

Specific gravity

Blood : 1.052 - 1.060
Plasma : 1.025 - 1.030
Cells : 1.088.

Specific gravity of blood rises in :
i. Lose of water from the body such as excessive sweating, diarrhoea, cholera etc.
ii. When water intake is inadequate.
iii. Exudation of fluid into tissue of serous cavity due to inflammation, surgical operation, burn etc.

Specific gravity falls in:
i. When a large quantity of water is taken.

ii. Injection of saline, glucose into vein.
iii. Immediately after severe haemorrhage, there is shift of tissue fluid into blood causing haemodilatation.

Hydrostatic pressure

In arterial end of capillary : 32 mm of Hg.
In venous end of capillary : 15 mm of Hg.

Function of blood :

1. *Transport of respiratory gasses :* It carries O_2 from alveoli of the lungs to the tissues and eleminates CO_2 from the tissue to the alveoli of the lungs.
2. *Transport of nutrients :* It carries digestive food materials absorbed by the intestine to the tissue cells i.e. glucose, amino-acid, fatty acid etc.
3. *Acts as vehicle :* Hormones, enzymes, vitamins & other chemicals are brought to their places of activity through blood stream.
4. *Regulation of body temperature :* Blood has high water content, water make it very suitable for this property due to
   a. High specific heat
   b. High thermal conductivity
   c. High latent heat of vaporization.
5. *Regulation of water and electrolytes balance:* Fluid portion of blood is interchangable with the intercellular fluid of the tissue, thus maintains water and electrolyte balance.
6. *Maintenance of acid base balance :* By efficient buffering power and with the help of kidney, skin, lungs etc blood maintains acid base balance.
7. *Defensive function :*
   a. WBC by its phagocytic properties engulf bacteria and foreign particles.
   b. It develops antibodies which combat toxic agent.
8. *Excretory function :* The metabolic end products and other waste products are carried by blood to the organ of excretion i.e. Kidney. Lungs, Skin etc.
9. *Regulation of blood pressure :* It regulate blood pressure by changing volume and viscosity of blood.
10. *It maintains colloidal osmotic pressure :* By the action of plasma proteins.
11. *Prevent haemorrhage :* By the process of coagulation it prevent haemorrhage.

Plasma

The fluid portion of the blood, the *plasma*, is a remarkable solution containing an immense number of ions, inorganic molecules, and organic molecules that are in transit to various parts of the body or aid in the transport of other substances. The normal plasma volume is about 5% of body weight, or roughly 3500 mL in a 70-kg man. Plasma clots on standing, remaining fluid only if an anticoagulant is added. If whole blood is allowed to clot and the clot is removed, the remaining fluid is called *serum*. Serum has essentially the same composition as plasma except that its flbrinogen and clotting factors II, V, and VIII have been removed and it has a higher serotonin content because of the breakdown of platelets during clotting.

(Ref. Ganong 22th Edition; Page-539)

Measurement of plasma volume

Indicators Used : Plasma volume can be measured by using indicators are-

1. Evans blue dye (also called, T-1824)
2. Serum albumin labelled with radio-active iodine (^{125}I-albumin).

(Ref. Guyton & Hall-11th Edition; Page-296)

Procedure : Suppose 10 ml of venous blood of a subject is taken in a heparinized tube. This serves as the control sample. 5 ml of a 5% solution of Even's blue (T-1824) in diluted water is then injected intravenously. 10 minute after the injection another 10 ml of sample is withdrawn from the vein into another heparinized tube. The haematocrit of both sample are determined. The optical density of the dye stained plasma is estimated. 0.01 ml of the dye is then diluted to 5 ml (dilution is 1 : 500) with the control plasma and its optical density is measured.

So plasma volume (ml)

$$= \text{Dye solution injected} \times \text{dye Solution stadarisation} \times \frac{\text{Density of standard}}{\text{Density of unknown}}$$

Calculation of interstitial fluid volume

Interstitial fluid volume cannot be measured directly but it can be calculated as-

$$\text{Interstitial fluid volume} = \text{Extracellular fluid volume} - \text{Plasma volume}$$

Measurement of blood volume

The avreage blood volume of a normal adult man is approximately 5,000 ml. On the average approximtely 3000 ml of this is plasma and remainder 2000 ml is blood cells.

Here plasma volume is obtained same as ECF.

$$\text{Total blood volume} = \frac{\text{Plasma volume}}{1 - \text{Hematocrit}}$$

For example, if plasma volume is 3 liters and hematocrit is 0.40, then total blood volume would be calculated as

$$\text{Total blood volume} = \frac{3}{1 - 0.40}$$

$$= 5 \text{ liters}$$

Another way to measure blood volume is to inject into the

which is normally only onethird saturated with iron, now becomes almost fully bound with iron, so that the transferrin accepts almost no new iron from the mucosal cells. Then, as a final stage of this process, the buildup of excess iron in the mucosal cells themselves depresses active absorption of iron from the intestinal lumen.

2. When the body already has excess stores of iron, the liver decreases its rate of formation of *apotransferrin,* thus reducing the concentration of this iron-transporting molecule in the plasma and the bile. Therefore, less iron is then absorbed by the intestinal apotransferrin mechanism, and less iron can also be transported away from the intestinal epithelial cells in the plasma by plasma transferrin.

Yet, despite these feedback control mechanisms for regulating iron absorption, when a person eats extremely large amounts of iron compounds, excess iron does enter the blood and can lead to massive deposition of hemosiderin in the reticuloendothelial cells throughout the body. At times, this can be very damaging.

(Ref. Guyton & Hall-11th ed, Page 426)

Erythrocytic sedimentatin rate (ESR)

Definition : When the blood is mixed with a suitable anticoagulant and is made to stand vertically, red blood corpuscles settle down to the bottom. The rate at which this sedimentation of red cells take place is known as erythrocytic sedimentatin rate (ESR).

Normal count :

1. Westergren method :
   Male : O to 6 mm in Ist hour
   Female : O to 12 mm in Ist hour.
2. Wintrobe method :
   Male : O to 12 mm in Ist hour.
   Female : O to 18 mm in Ist hour.

Importance of ESR :

1. To see the prognosis of disease.
2. To assay the condition of some chronic inflammatory diseases, such as :
   i. Pulmonary tuberculosis
   ii. Pulmonary embolism
   iii. Myocardial infarction
   iv. Coronary thrombosis
   v. Rheumatic arthritis
   vi. Carcinoma.
3. To see the therapaeutic effects of drugs.

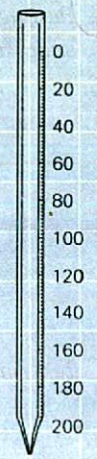


Fig. 5-2. *Westergren ESR tube*

ESR increases in

A. *Physiological conditions :*
   i. During menstruation
   ii. During pregnancy
   iii. In high atmosphere pressure.

B. *Pathological conditions :*
   1. Multiple myeloma
   2. Tuberculosis
   3. Rheumatic arthritis
   4. Chronic inflammation
   5. Malignancy
   5. Coronary thrombosis
   7. Haemorrhage
   8. Pregnancy
   9. Toxaemic condition
   10. SLE.
   11. Other types of tissue necrosis

ESR falls in :

A. Phygiological condition :
   i. In high altitude
   ii. In dehydration
   iii. In defect of rouleaux formation.

B. Pathological condition :
   i. Haemocromatosis
   ii. Polycythemia vera.

Estimation of ESR

There are two methods for estimatin of ESR :

i. Westergren method.
ii. Wintrobe method.

Westergen method

Materials required :

1. Westergren tube : It is a straight glass tube, 30 cm. in length and 2.5 mm in diameter. It is calibrated in m.m. from 0 to 200. Both ends of tube are open.
2. Westergren tube-rack.
3. Test tube
4. Reagent : 3.8% sodium citrate solution (anticoagulant).
5. Blood collecting meterials.

Steps :

1. Take 0.4 ml reagent in a test tube.
2. Draw venous blood and add 1.6 ml blood in the test tube.
3. Draw mixed blood in the westergren tube by sucking by the mouth upto the mark 'O'.
4. Place the tube in the rack in vertical position with the zero mark above.
5. Take the reading after one hour by noting down the level of lower end of the clear plasma.

Precautions to be taken :

1. The tube must be in perfect vertical position.

2. The reagent and the blood must be mixed in correct proportions.
3. The test must be made within one hour after the collection of the blood.

Wintrobe Method

Materials required :

1. Wintrobe tube : It is a straight tube, 110 mm in length and 2.5 mm in diameter. It is graduated in mm with double rows, 0 - 100 and 100 - 0; 0 - 100 for ESR and 100 - 0 for PCV. One end of the tube is open and another is closed.
2. Reagent : Paul-Heller mixture- 6 mg of Ammonium oxalate and 4 mg of potassium oxalate for 5 ml of blood.
3. Test tube.
4. Blood collecting materials.

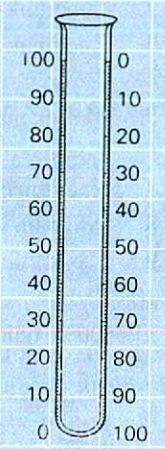


Fig.5-3. *Wintrobe ESR tube.*

Steps :

1. Collect one to five ml of blood and transfer to the tube containing the anticoagulant in the proportion of 1-2 mg of dry powder for each ml. of blood.
2. Draw one ml of blood in a capillary tube and fill the wintrobe tube upto 100 mark (0) from the bottom.
3. Place the tube in vertical position and take the reading after one hour.

Factors influence the ESR

The factors involved in the rate of fall of the RBC influence the ESR. These are :

1. *Factors which increase rouleaux formation and viscosity of plasma enhance ESR :*
   a. Increase plasma fibrinogen.
   b. Increase plasma globulins.
   c. Decrease plasma albumin.
   d. Decrease plasma Hb. conc. (Anaemia)
   e. Increase dilution of blood.
   f. Decrease number of RBC.
2. *Technical and instrumental factors also influence ESR :*
   a. Position of ESR tube : Properly vertical tube gives accurate reading. Any degree of inclination increase ESR.
   b. Quantity of anticoagulant used : Excess potassium oxalate and sodium citrate increase and decrease the ESR value respectively.
   c. Delay in the test : If the test is delayed after collection of blood, ESR becomes high.
   d. Room temperature : With the rise of room temperature ESR is raised.
   e. Method of determination : The length and diameter of the ESR tube influence the value. Hence the value is more in wintrobe method than the westergren method.

Rouleaux formation

It is a special process of sedimentation of RBC by which RBC settle one at the top of the others, so that the ratio of mass and surface area increased. It depends upon-

i. Fibrinogen & globulin number
ii. Tissue destruction
iii. Albumin number.

Anaemia

Definition : Anaemia may be defined as a reduction of haemoglobin concentration per unit volume of peripheral blood below normal for the age and sex of the patien which is usually but not invariably associated with the reduction of RBC.

(Ref. Clinical pathology)

Cause of anaemia :

1. Excessive blood loss due to acute or chronic haemorrhage
2. Reduced production of RBC due to lack of some factors which are necessary for RBC production.
3. Excessive blood cell destruction in comparision to the production of blood cells
4. Destruction of bone marrow.

Site of observation of Anaemia :

1. Lower palpebral conjunctivae
2. Dorsal surface of the tongue
3. Oral mucous membrane
4. Skin of the hands
5. Skin of the sole of the feet.

Classification of anaemia

A. ***Pathogenetic & Aetiological :*** (According to the cause of anaemia)

1. *Anaemia due to blood loss :*
   a. Acute post haemorrhagic : May be due to trauma, accident & causes normocytic or slight macrocytic normochromic anaemia.
   b. Chronic post haemorrhagic e.g chronic blood loss due to hookworm infestation. Initially causes normocytic normochromic anaemia & later, hypochromic microcytic anaemia.
2. *Anaemia due to impaired red cell formation :*
   a. Anaemia due to disturbance of bone marrow function *due to deficiency of erythropoietic factors :*
      i. Iron deficiency anaemia (commonest)
      ii. Megaloblastic anaemia
      iii. Anaemia associated with scurvy

iv. Anaemia due to protein malnutrition (rare).

b. Anaemia due to disturbance of bone marrow function not *due to deficiency of substances essential for erythropoiesis :*

i. Anaemia associated with infection, renal failure, liver disease, disseminated malignancy, collagen disease, bone marrow infiltration, leukaemia, malignant lymphoma, multiple myeloma, myelosclerosis etc.

ii. Aplastic anaemia.

iii. Sideroblastic anaemia.

iv. Anaemia associated with myxoedema & hypopituitarism.

v. Congenital diserythropoietic anaemia.

3. *Anaemia due to increased red cell destruction :*

a. Haemolytic anaemia due to corpuscular defect.

b. Haemolytic anaemia due to abnormal haemolytic mechanism (extracorpuscular defect).

B. ***Morpholoical :*** (Based on the characteristics of the red cell as determined by blood examination mainly MCV & MCHC).

1. *Normocytic normochromic anaemia* e.g. aplastic anaemia, acute post haemorrhagic anaemia.
2. *Microcytic hypochromic* e.g. Iron deficiency anaemia, Thalassaemia.
3. *Macrocytic anaemia* e.g. Megaloblastic anaemia.
4. *Simple microcytic.*

Effect of anaemia :

One of the major effects of anaemia is greartly increased work load on the heart. Due to increased venous return caused by-i. decreased viscosity of blood. ii. Diminished transport of oxygen by the blood causes tissue vessels to dilate.

Iron deficiency anaemia

Aetiology & pathognesis of iron deficiency anaemia. :

Major aetiologic factors :

1. In females in the reproductive period of life :
   a. Menstruation
   b. Pregnancy
   c. Pathological blood loss
   d. Defective diet.
2. In adult males & post-menopausal females :
   a. Pathological blood loss.
3. In infants & children :
   a. Defective diet
   b. Diminished iron stores at birth.

Pathogenesis : When the supply of iron to the bone marrow is insufficient for the requirements of Hb synthesis, iron deficiency anaemia takes place.

Iron deficiency may be regarded as developing in two stages

1. Progressive depletion of the available tissue iron stores.
2. Ultimate exhaustion of the available tissue iron stores, followed by the development of anaemia.

There are 4 major factors in the pathogenesis of iron deficiency anaemia :

1. An increase physiological demand for iron.
2. Loss of blood.
3. Inadequate iron intake.
4. Impaired absorption of iron.

Increase physiological demand :

1. In children : During the period of growth there is a progressive increase in the blood volume & consequently in the total amount of Hb in the body, this result in an increase demand for iron by the marrow for hemoglobin synthesis.
2. In female ; During the reproductive life due to menstruction, (blood loss- 15-30 mg/month), pregnancy (requires 500-600 mg for foetus), parturition, and lactation(180 mg).

Blood loss :

1. From GIT : Bleeding peptic ulcer, Hook worm infestation,Carcinoma stomach, Rupture of oesophageal varies, Hiatus hernia, Haemorrhoids, Carcinoma colon, Ulcerative colitis, Chronic aspirin ingestion & Piles.
2. From respiratory tract : Any condition associated with haemoptysis e.g Pulmonary tuberculosis., Bronchogenic carcinoma.
3. From urinary tract : Any condition associated with haematuria e.g calculi in urinary tract.
4. From uterus : menorrhagia, uterine fibroid, Carcinoma cervix or uterus.
5. Wide spread bleeding disorder e.g Haemophilia, purpua etc.

Inadequate intake of iron :

1. In infant : milk injury, improper feeding.
2. In adult : Anorexia, poverty, dietary dislike.

Impaired absorption :

Coeliac disease, Sprue, Diarrhoea. Achlorhydria, Total or partial gastrectomy, Atopic gastritis, following gastroenterostomy.

Aplastic anaemia

Definition : Aplastic anaemia may be defined as a disorder characterised by the occurance of anaemia, leucopenia and thrombocytopenia, resulting from aplasia of the bone marrow.

Classification :

A. Primary or idiopathic

B. Secondary or symptomatic : caused by physical or chemical agents.

C. Miscellenous :
   1. Familial hypoplastic anaemia (Fanconi's syndrome).
   2. Aplastic anaemia associated with infective hepatitis.
   3. Aplastic anaemia associated with pancreatic insufficiency.
   4. Aplastic anaemia associated with paroxysmal nocturnal haemoglobinuria.

D. Pure red cell aplasia (erythroblastopenia) :
   1. Congenital
   2. Acquired (with or without associated thymoma).

Aetiology

a. Drugs :
   i. Drugs which regularly cause bone marrow depression: N-mustard, busulphan, chloram bucil, vincristine etc.
   ii. Drugs which rarely cause bone marrow depression: Oxyphenbutazone, chloram phenicol, tolbutamide, chlordizaepoxide, aloxidone.

b. Chemicals : Benzene, TNT, lindane, DDT, chlordane.

c. Physical agents : X-ray, gamma-ray, neutrons, a & b ray.

Megaloblastic anaemia

Definition : The anaemias which are characterised by distinctive cytologic and functional abnormalities in peripheral blood and bone marrow cells due to impaired DNA synthesis as a result of vitamin B_{12} or folic acid deficiency or both are known as megaloblastie anaemias.

Causes :

A. *Causes of vitamin B_{12} deficincy :*
   1. Less intake :
      Nutritional deficiency.
   2. Impaired absorption :
      a. Gastric :
         i. Pernicious anaemia - due to lack of intrinsic factor of castle.
         ii. Total or partial gastrectomy.
      b. Intestinal causes :
         i. Coeliac disease
         ii. Tropical sprue
         iii. Fish tape (Dyphylobothrium latum) worm infestation.
      c. Chronic pancreatic disease.
      d. Interference with normal absorption by bacteria or parasites.
   3. Drugs :
      a. Para amino salicylic acid
      b. Metformin
      c. Neomycine.
   4. Vit. B_{12} deficiency in child hood :
      a. Juvenile pernicious anaemia
      b. Congenital intrinsic factor deficiency.

B. *Causes of folic acid deficiency :*
   1. Less intake :
      a. Nutritional deficiency.
   2. Impaired absorption :
      a. Coeliac disease
      b. Tropical sprue.
   3. Increased demand :
      a. Pregnancy
      b. Puerperium
      c. Haemolytic anaemia
      d. Leukaemia
      e. Lymphoma
      f. Malignancy
      g. Sideroblastic anaemia
      h. Inflammatory disorders
      i. Hyper thyroidism
      j. Skin disease
   4. Drugs : Anti convulsant, Oral contracetive, Methotrexate, trimethoprim, triamterene, Pyrimethamine.

Haemolytic anaemia

Definition :

A haemolytic anaemia may be defined as an anaemia resulting from an increase in the rate of red cell destruction.

Classification :

A. *Haemolytic Anaemias due to intracorpuscular defects :*
   1. Congenital :
      a. Due to membrane defects :
         i. Hereditary spherocytosis
         ii. Hereditary eliptocytosis.
         iii. Hereditary stomatocytosis.
      b. Due to Hb. defect :
         i. Haemoglobinopathies e.g sickle cell anaemia, unstable Hb. disease.
         ii. Thalassaemia (b-thalassaemia major, Hb–H disease)
      c. Due to enzyme defect :
         i. Non-spherocytic congenital haemo- lytic anaemia
            Due to deficiency of pyruvate kinase
            Due to deficiency of glucose- 6- phosphate dehydrogenase.
         ii. Drug induced haemolytic anaemia & favism.
   2. Acquired :
      a. Paroxysmal nocturnal haemoglobinuria

B. *H. anaemias due to extra corpusclar defects.*

1. Immune mechanisms :
   a. Autoimmune acqired haemolytic anaemia (Warm & cold antibody)
   b. Haemolytic disease of the newborn erythroblastosis foetalis
   c. Incompatible blood transfusion.
   d. Drug induced haemolytic anaemia.
2. Non-immune mechanisms :
   a. Mechanical haemolytic anaemia
      i. Cardiac haemolytic anaemia
      ii. Microangiopathic A.
   b. Misc :
      i. Haemolytic anaemia due to direct action of drugs and chemicals.
      ii. Haemolytic anaemia due to infection.
      iii. Haemolytic anaemia due to burns.
      iv. Lead poisoning.

Pernicious anaemia

Pathogenesis : The fundamental defect in pernicious anaemia is a failure of secretion of intrinsic factor by the stomach due to permanent atrophy of the gastric mucosa. Gastric atrophy is the end result of complex interaction between genetic and autoimmune factors.

Gastric atrophy → Reduced intrinsic factor secretion → failure of absorption of dietary Vit. B_{12} → deficiency of Vit. B_{12} → give rise to following C/F.

Clinical features :

a. *Common :*
   1. Megaloblastic macrocytic anaemia
   2. Glossitis.
   3. Peripheral neurophathy & subacute combined degeneration of spinal cord.

b. *Less common :*
   1. Angina of effort
   2. CCF (Congestive cardiac failure)
   3. Recurrent diarrhoea
   4. Dyspepsia, anorexia & weight loss.
   5. Mental disturbances
   6. Visual disturbances.

Age : Middle & older age groups.

Thalassaemia

Definition : The thalassaemias are a heterogenous group of disorders in which there is a genetically determined reduction in the rate of synthesis of one or more types of normal hemoglobin. polypeptide chains resulting in a decrease production of hemoglobin having the affected chain.

Classification :

A. *Haematological :*
   1. α thalassaemia : affecting the synthesis of a chain.
   2. β Thalassaemia : affecting the synthesis of b chain.
      a. β^+ Thalassaemia : incomplete suppression of beta chain synthesis.
      b. β^o Thalassaemia : complete absence of beta chain synthesis.

B. *Clinical :*
   1. Thalassaemia major or cooley's anaemia : Total suppression of beta chain synthesis and it is the homozygous form of the disease.
   2. Thalassaemia minor or trait : Heterozygous form of the disease.

Clinical features :

1. Pallor, diarrhoea & recurrent fever.
2. Hepatomegaly & spleeno-megaly.
3. Slow growth in childhood.
4. Mongoloid face.
5. Severe anaemia.
6. Epistaxis, skin pigmentation, etc.

(Ref. Clinical pathology)

Differences between thalassaemia & iron deficiency anaemia.

Thalassaemia	*Iron-deficiency anaemia*
1. Congenital	1. Acquired
2. Break down of RBC prominent	2. Not present
3. Nucleated RBC plenty	3. A few nucleated RBC in severe case
4. Serum iron increased	4. Serum iron decreased
5. Serum iron binding capacity reduced.	5. Serum iron binding capacity increased.

Haemoglobinopathies

Definition : When possession of Hb variant gives rise to a clearly defined disease state, the affected person is said to have a haemoglobinopathy. The haemoglobinopathies are characterised by the production of structurally abnormal Hb due to abnormalities in the formation of the globin moiety of the molecule.

Types :

1. Hb..S sickle haemoglobinopathies
2. Hb..C sickle haemoglobinopathies
3. Hb..E sickle haemoglobinopathies

4. Hb..D sickle haemoglobinopathies
5. The unstable Hb haemoglobinopathies
6. Haemoglobinopathies associated with polycythemia.

Most of the abnormal Hbs produce no harmful effect and the individual remains asymptomatic and unware of the abnormality within red cells. The abnormal Hbs are inherited as autosomal codominants.

The subjects who inherit one abnormal and one normal gene are called *heterozygotes*. The X subjects who inherits two identical abnormal genes are called *homozygotes*. The *homozygous* state is usually referred to as the 'disease' e.g Hb-C disease and the *heterozygous* state is as the 'trait' e.g sickle cell trait.

(Ref. Clinical Pathology)

Q. ***Write down the laboratory investigation of haemoglobinopathies.***

Ans.

1. *Routine haematological and biochemical test* :
   a. Hb estimation
   b. PCV
   c. TC of RBC
   d. Reticulocyte count
   e. Determination of red cell indices
   f. Examination of the blood film
   g. Bilirubin estimation
   h. Other biochemical tests for the presence of haemolysis.
2. *Test depending on physio-chemical properties of abnormal haemoglobin* :
   a. Sickle test
   b. Hb solubility test
   c. Demonstration of intracellular crystal, Hb H inclusion etc.
   d. Heat instability test
   e. Isopropanolol precipitation test
   f. Oxygen dissociation studies
3. Hb electrophoresis for the demonstration of abnormal Hb
4. Alkali denaturation
5. The acid elution test.

(Ref. Clinical Pathology)

Sickle cell anaemia

The sickle haemoglobinopathies are hereditary disorders in which the red cells contain Hb–S.

Definition : It is a hereditary disorder where there is anaemia due to the presence of Hb–S in red cells.

Types :

1. Sickle cell anaemia (homozygous state)
2. Sickle cell trait (heterozygous state).

Pathogenesis : In sickle cell anaemia red cells containing Hb–S differs from Hb–A in substitution of valine for glutamic acid in the 6th position from the N -terminal end of the beta chain. In the deoxygenated state, the conformational changes in Hb–S are tactoid formation. As a result the red cells containing Hb–S, become rigid and deformed to assume a sickle or crescent shape. Red cells will begin to sickle at an O_2 tension of 50 to 60 mm of Hg. This tension is experienced by the cells in parts of microcirculation and thus sickling occurs in vivo. If the flow rate is rapid, sickling does not become fully established and the cells resume normal shape when they are swept back to areas of the circulation where the oxygen tension is higher. If the flow rate is slow and the cells are delayed in areas where the O_2 tension is low, the cells sickle and there is a great increase in blood viscosity with further slowing of circulation.

The sickling of the red cells in the circulating blood has two major ***pathological effects :***

1. The distorded cells cause a great increase in blood viscosity and block small blood vessels, impairing flow and causing ischaemia and infarction of the tissue.
2. Repeated "sickle-unsickle" cycle leads to loss of fragments of red cell membrane and the cells become spherocytic and fragile.

They are removed by R.E. system and to a lesser extent destroyed in the circulation resulting in both extravascular and intravascular haemolysis leading to anaemia.

Hereditary spherocytosis :

In this condition, the RBC are small in size, spherical in shape rather than biconcave. They can not compressed because they do not have the normal loose bags like structure. There fore, on passing through the small capillaries they easily ruptures and causes anaemia.

Polycythemia

Definition : Polycythaemia is defined as an increase in the concentration of red cells, above the normal for the age & sex of the patient.

Secondary polycythemia : Whenever the tissues become hypoxic because of too little oxygen in the atmosphere, such as at high altitudes, or because of failure of delivery of oxygen to the tissues, as occurs in cardiac failure, the blood-forming organs automatically produce large quantities of extra red blood cells. This condition is called *secondary polvcvthemia*, and the red cell count commonly rises to 6 to 7 million/mm^3, about 30 per cent above normal.

A common type of secondary polycythernia, called *physiologic polycvthemia*, occurs m natives who live at altitudes of 14,000 to 17,000 feet. The blood count is generally 6 to 7 million/mm^3 this is associated with the ability of these people to perform high levels of continuous work even in a rarefied atmosphere.

(Ref. Guyton & Hall-11th ed; Page 427)

Polycythemia Vera (Erythremia) : In addition to those people who have physiologic polycythemia, others have a pathological condition known as *polycythemia vera*, in which the red blood cell count may be 7 to 8 million! mm^3 and the hematocrit 60 to 70 per cent.

Causes of polycythemia vera : Polycythemia vera is caused by a genetic aberration that occurs in the hemocytoblastic cell line that produces the blood cells. The blast cells no longer stop producing red cells when too many cells are already present. This causes excess production of red blood cells in the same manner that a tumor of a breast causes excess production of a specific type of breast cell. It usually causes excess production of white blood cells and platelets as well.

Effect : In polycythemia vera, not only does the *hematocrit increase*, but the *total blood volume also increases*, on some occasions to almost twice the normal level. As a result, the *entire vascular system becomes intensely engorged.* In addition, many of the *capillaries become plugged* by the viscous blood because the viscosity of the blood in polycythemia vera sometimes increases from the normal of 3 times the viscosity of water to 10 times that of water.

(Ref. Guyton & Hall-11th ed; Page 428)

Causes of polycythaemia :

A. *True or absolute polycythaemia :* There is an increase in the total red cell volume of the body relative to body weight.
   1. Idiopathic polycythaemia vera (erythraemia or aquez-Osler disease)
   2. Secondary polycythaemia (erythrocytosis)
      a. Secondary to hypoxia :
         i. High altitude
         ii. Congenital heart disease
         iii. Chronic pulmonary disease
         iv. Miscellaneous (rare)

         Aquired heart disease, disorder associated with alveolar hypoventilation :
         a. Emphysema
         b. Diffuse pulmonary fibrosis, Abnorm alities of pigment metabolism.
      b. Secondry to increased erythropoietin production.
         i. Non neoplastic kidney disease : Cysts, hydronephrosis.
         ii. Tumours : Kidney, liver etc.
         iii. Ovarian tumour
         iv. Leiomyoma of uterus
         v. Pheochromocytoma.
   3. Benign familial polycythaemia.
   4. Polycythaemia associated with haemoglobino pathies (compensatory polycythaemia)

B. *Relative polycythaemia :* Here total red cell volume is within the normal range. But there is increase RBC concentration or increase PCV due to haemo concentration as evidenced by :
   1. Dehydratin : fluid loss or diminished intake.
   2. Redistribution of body fluids
   3. Pseudopolycythaemia (Polycy-thaemia of stress, Spurious polycythaemia)
   4. Adrenal insufficiency : (increase loss of electrolyte Æ increase loss of fluid).
   5. Shock.

Effect of polycythemia:

1. *On circulatory system :*
   a. Because of greatly increased viscosity of the blood in polycythemia, the flow of blood through the vessels is often sluggish. It is obvious that increasing the viscosity tends to decrease the venous return. On the other hand, the blood volume is greatly increased, in polycythemia, which tends to increase the venous return. Actually, the cardiac out put in polycythemia is not far from normal because these two factors more or less neutralize each other.
   b. The arterial pressure is normal in most persons with polycythemia. Because, the blood pressure regulating mechanisms can usually offset the tendency for increased blood viscosity to increase peripheral resistance and there by to increase arterial pressure.
2. *On skin colour :*
   a. In secondary polycythemia, cyanosis is almost always evident.
   b. In polycythemia vera , ordinarilly has a ruddy complexion but may at times have a bluish (cyanotic) tint to the skin.

(Ref. Guyton & Hall-11th edition; Page 428)

***Summary** : Effect of polycythemia*

1. Blood viscosity increased.
2. Blood volume increased.
3. Cardiac out put more or less normal.
4. The arterial pessure usually normal.
5. Cyanosis presenl.

Jaundice

Definition : When free or conjugated bilirubin accumulates in the blood, the skin, sclera and mucous membranes turn yellow. This yellowness is known as jaundice (icterus) and is usually detectable when the total plasma bilirubin is greater than 2 mg/dl (34 μmol/L).

(Ref. Ganong 22th edition, Page 503)

Normal serum bilirubin level :

a. Normal level : 0.2-0.8 mg/100 ml (dl) of blood.
b. In new born : 0.2-5.9 mg/100 ml (dl) of blood.

High level of serum bilirubin in infant is due to excessive break down of RBC and failure of immature liver to metabolise such.

Latent jaundice : Serum bilirubin level is 0.8-2 mg/100 ml.

Clinicl jaundice : Serum bilirubin level is more than 2 mg%

Types :

1. Haemolytic or pre hepatic
2. Hepatocellular or hepatic
3. Obstructive or cholestatic or post hepatic.

Pathogenesis : Jaundice may develope due to any one of the following conditions :

1. Excess production of bilirubin (haemolytic anaemia, etc).
2. Decrease uptake of bilirubin into hepatic cells.
3. Disturbed intracellular protein binding or conjugation.
4. Disturbed secretion of conjugated bilirubin into the bile canaliculi.
5. Intrahepatic or extrahepatic bile duct obstruction.

(Ref. Ganong 22th Edition; Page-503)

Causes of jaundice

A. *Haemolytic jaundice :*
   1. Haemolytic anaemia e.g. Malaria, Eryth roblastosis foetalis, Thalassemia etc.
   2. Increase production of shunt bilirubin in the bone marrow.
   3. Massive haemorrhage within the body.

B. *Hepatocellular jaundice :*
   1. Reduced uptake of bilirubin by hepatic cells : Gilbert's disease, Drug induced etc.
   2. Impaired conjugation of bilirubin : Neonatal jaundice, Crigler-Najji syndrome, Gilbert's disease.
   3. Impaired excretion of conjugated bilirubin :
      a. Intrahepatic causes : Dubin-Johnson syndrome, Rotor syndrome, Drug induced (Oestrogen, steroid) etc.
      b. Extra hepatic causes : It occurs due to the obstruction of biliary tract. The obstruction may be in the lumen, in the wall or out side the tract :
         i. Lumen : Gall stone, Worm etc.
         ii. Wall : Cholengitis, Tumour, Atresia, Stricture etc.
         iii. Out side the wall : Ca of the head of the pancreas, Sub-hepatic abscess, Enlarged lymph node etc.
      4. Combination of all : Viral hepatitis, Septicaemia, Cirrhosis of liver, Hepatic poisoning etc.

C. *Obstructive jaundice* : Same as the intra and extra hepatic causes of impaired excretion of bilirubin in hepatocellular jaundice.

Vanden Bergh's Reaction

It is a test by which prehepatic and posthepatic jaundice are detected . Here diazo reagents are used containing-

i. Sulphanilic acid
ii. Sodium nitrite
iii. Hydrochloric acid.

Types :

1. Direct
2. Indirect
3. Biphasic

Procedure : 0.5 ml of diazo reagent is added to 0.5 ml of serum and then mixed.

Result :

1. *Direct :* When red colour appears immediately, it is due to conjugated bilirubin.
2. *Indirect :* If red colour does not appear within 30 mins. then 0.5 ml 95% alcohol is added and mixed. If red colour then appears, it is an indirect reaction & due to unconjugated bilirubin.
3. *Biphasic :* The reaction is direct but the colour depends on standing. It is due to both conjugated and unconjugated bilirubin.

Interpretation :

1. *Direct reaction :* Found in obstructive jaundice where bilirubin is conjugated in serum. The conjugated bilirubin is water soluble & can easily mix with diazo reagent to give colour immediately.
2. *Indirect reaction :* Found in haemolytic jaundice where bilirubin is unconjugated & water insoluble. Here bilirubin cannot directly mix with diazo reagent. But when alcohol is added it helps unconjugated bilirubin to mix with diazo reagent & then colour appears.
3. *Biphasc reaction :* Found in hepatocelluar jaundice because here both conjugated & unconjugated bilirubin is present.

Differences between conjugated and unconjugated bilirubin

Unconjugated bilirubin	*Conjugated bilirubin*
1. Water insoluble.	1. Water soluble
2. Vanden Bergh's reaction— Indirect positive.	2. Vanden Bergh's reaction— Direct positive.
3. In normal person present in blood.	3. In normal person absent in blood.
4. Not passes in urine.	4. It passes in urine.
5. Lipid soluble.	5. Lipid insoluble.
6. May cause CNS damage.	6. Do not cause CNS damage.

Laboratory findings of different types of jaundice

Points	*Haemolytic J.*	*Hepatocellular J.*	*Obstructive J.*
Urine			
a. Bilirubin	Absent	Variable	Present
b. Urobilinogen	Increase	Variable	Decrease
c. Bile salt	Absent	Absent	Present
Stool			
a. Colour	Dark	Normal or pale	Pale
b. Stercobilinogen	Increase	Decrease	Absent
c. Bile salt	Normal	Normal or decrease	Absent
d. Fat	Normal	Normal or increase	Increase
Blood			
a. Serum bilirubin	Incrase (mostly unconjugated)	Increase (both conjugated & unconjugated)	Increase (mostly conjugated)
b. Alkaline phosphatase	Normal	Increase	Marked increase
c. Serum aminotransferase.	Normal	Increase	Normal
d. Serum protein	Normal	Decrease	Normal
e. Prothrombin time	Normal	Increase	Increase
f. LDH	Normal	Increase	Normal

White Blood Corpuscle (WBC)

Definition : White blood corpuscles are the nucleated colourless cells of blood and are the mobile units of the body's protective system.

Morphology

1. Normal size : 10-20 Micron
2. Normal counts : 4000-11000/μL of blood
3. Life span : Few hours to few days.
4. Production : In bone marrow, spleen, tonsil etc. When WBC enters in the circulation from bone marrow they never come back to bone marrow. Again, when they enters in the tissue from circulation they never come back to the circulation.

In the bone marrow- RBC : WBC = 1 : 50
In the circulation- RBC : WBC = 500 : 1

(Ref. Ganong 22th edition; page-516 & others)

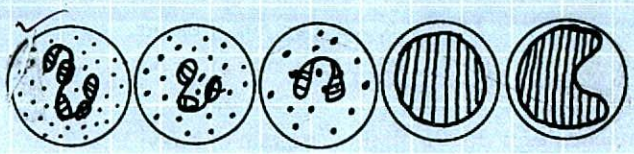
Life span of WBC :

The main reason white blood cells are present in the blood is to be transported from the bone marrow or lymphoid tissue to the areas of the body where they are needed. The life of the ***granulocytes*** once released from the bone marrow is normally 4 to 8 hours circulating in the blood and anthour 4 to 5 days in the tissues. In times of serious tissue infection, this total life span is often shortened to only a few hours becasue the granulocytes then proceed rapidly to the infected area, perform their functions, and in the process are themselves destroyed.

The ***monocytes*** also have a short transit time, 10 to 20 hours, in the blood before wandering through the capillary membranes into the tissues. Once in the tissues they swell to much larger sizes to become ***tissue macrophages***, and in this form, they can live for months or even years unless they are destroyed by performing phagocytic function. These tissue macrophages form the basis of the tissue macrophage system, that provides a continuing defense in the tissues against infection.

Lymphocytes enter the circulatory system continually along with the drainage of lymph from the lymph nodes and other lymphoid tissue. Then, after a few hours, they pass back into the tissues by diapedesis and then re-enter the lymph and return either to lymphoid tissue or to the blood again and again; thus, there is continual circulation of the lymphocytes through the body. The lymphocytes have life spans of weeks, months, or even years, but this debends on the body's need for these cells.

Ref. Guyton & Hall-11th edition; Page 431)



Neutrophil Eoinophil Basophil Lymphocyte Monocyte

Fig. 5-7. *Different types of WBC.*

Types of WBC :

On the basis of presence or absence of granules in the cytoplasm WBC are of two types

1. *Granulocytes :* Having granules in cytoplasm. Granulocytes on the basis of nucleus staining and size of the granules are of three types-
   a. Polymorphonuclear neutrophils
   b. Polymorphonuclear eosinophils
   c. Polymorphonuclear basophils.
2. *Agranulocytes :* Having no granules in cytoplasm. They again divided into two types -
   a. Lymphocytes
   b. Monocytes
3. Occationally, *plasma cells.*

N.B *The granulocytes and monocytes protect the body against invading organisms mainly by phagocytosis. The lymphocytes and plasma cells function mainly by in connection with immune system.*

(Ref. Guyton & Hall-11th edition; Page 430)

Normal values of WBC or *nomal count of WBC :*

1. Per microliter of blood : 9000 cells
   Approximate range : 4000-11000 cells.

(Ref. Ganong 22th Edition; Page 516)

1. Per microliter of blood : 7000 cells.

(Ref. Guyton & Hall-11th edition; Page 430)

Differential count of WBC

Neutrophils	:	50-70 %
Eosinophils	:	1-4 %
Basophils	:	0-0.4 %
Lymphocytes	:	20-40 %
Monocytes	:	2-8 %

(Ref. Ganong 22th Edition; Page 516)

Differential count of WBC (approximate average) :

Neutrophils	:	62.0 %
Eosinophils	:	2.3 %
Basophils	:	0.4 %
Lymphocytes	:	30.0 %
Monocytes	:	5.3 %

(Ref. Guyton & Hall-11th edition; Page 430)

Absolute count of WBC

Neutrophils	:	3,000 - 6,000 /cu. mm of blood
Eosinophils	:	150 - 300 /cu. mm of blood
Basophils	:	0 - 100 /cu. mmof blood
Lymphocytes	:	1500 - 4000 /cu. mm of blood
Monocytes	:	300 - 600 /cu. mm of blood.

(Ref. Ganong 22th Edition; Page-516)

Function of WBC

1. *Phagocytosis :* By this process WBC engulf bacteria, other foreign particles and micro-organism.
2. *Antibody formation :* Lymphocytes produce antibody and play an important role in defensive mechanism of the body.
3. *Secretion of heparin :* Basophil secretes heparin which prevents intravascular clotting.
4. *Formation of fibroblasts :* Lymphocytes may be converted into fibroblasts in the area of infection and thus help the process of repair .
5. *Anti-histamine function :* Eosinophil produces 5 HT.
6. *Chemotaxis :* Leucocytes have chemotactic properties by which they migrate out of the vessels to the site of injury by amoeboid movement.
7. *Act as scavanger :* By removing debris of dead and devitalized tissues they do the job of scavengers.

Properties of WBC

1. *Diapedesis :* It is the process by which WBC (Neutrophil and Monocytes) comes out through the pores of the blood vessels by squeezing. WBC comes to the vessel wall then small portion of the cell sque eze through the pores of the blood vessel then the squeezing continues and finally WBC comes out the blood ves sel.
2. *Ameboid movement :* It is a special type of movement by which WBC(Neutrophil and macrophages) moves towards the damaged tissue. The rate of movement is 40 micron per

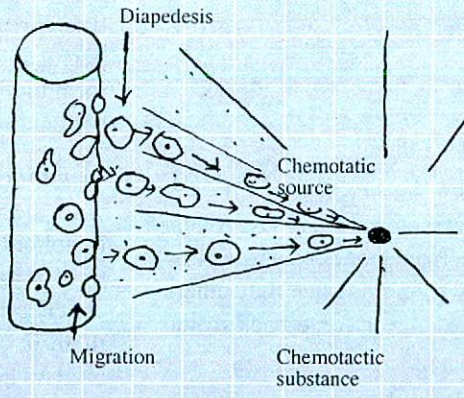


Fig. 5-9. *Diapedesis*

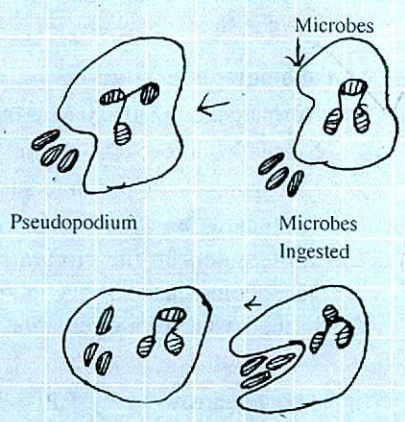


Fig. 5-10. *Phagocytosis*

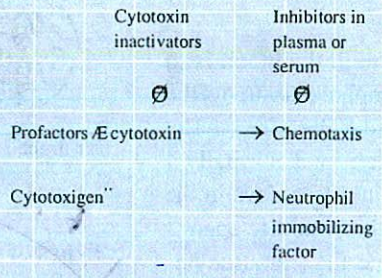


Fig. 5-11. *Chemotaxis*

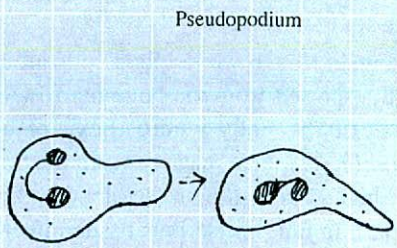


Fig. 5-12. *Ameboid Movement*

minute. Ameboid movement begins with protrution of a pseudopodium from one end of the cell. The pse- udopodium projects far out , away from the cell body and then the remainder of the cell moves toward the pseudopodium. This occurs due to continual changes of jel to sol within the cytoplasm of the cell.

3. *Chemotaxis :* A number of different chemical substances liberated by damaged tissue cause both neutrophil & macrophages to move toward the source of the chemical. This phenomenonis known as chemotaxi s. This chemical substances which either attract the WBC is called chemotaxic substance.

   These include :

   i. Bacterial toxins
   ii. Degenerated products of the inflamed tissues.
   iii. Components of complement complex
   iv. Several reaction products caused by plasma clotting in the inflamed area.

   Chemotaxis is effect upto 100 micrometers away from an inflammed tissue.

4. ***Phagocytosis :*** It is the process by which WBC(Neutrophil and macrophages) engulf foreign particles. It depends upon

   a. Rough surface of the foreign particles
   b. Surface charge of the foreign particles must be positive.
   c. Opsonin - It is globulin protein. It combines with dead tissue and foreign particles and help in phagocytosis.

   Mechanism : Phagocytosis involve 3 distinct steps :

   i. Recognition & attachment : Neutrophils & macrophages first rcognise the particles to be ingested and attach on their surface.
   ii. Engulfment : After attachment the phagocytic cells produce pseudopodes around the particle & completely enclose it. At this stage, the particle is enclosed in a membrane bound cytopasmic vesicle called phago-some.
   iii. Killing and/ or degradation: After engulfing most organisms destroyed with in the phagosome by the lysosomal enzyme.

Neutrophil

Its granules take either acidic or basic stain.

Character :

i.	Cell size	: 10 - 15 micron.
ii.	Nucleus	: Multilobed (3-6 lobed).
iii.	Granules	: Fine, uniformly distributed.
iv.	Cytoplasm	: Reddish-brown or violet in colour.
vii.	Life span	: Average 6 hours in the circulation
viii.	Production	: 100 billion neutrophils/day.

Functions :

1. They engulf bacteria by phagocytic activity.
2. They secrete proteolytic enzymes which digest the ingested particles causes degradation of tissue & thus hasten the process of recovery.
3. They collect at the site of infection by chemotactic properties.
4. It act as a first line defence aganist pyogenic infection.
5. They liberate chemotactic factor for macrophage.

Eosinophil

Its granules take acid stain.

Character :

i.	Cell size	: 10 - 12 micron.
ii.	Nucleus	: Bi or tri-lobed.
iii.	Granules	: Coarse, uniformly distributed.
iv.	Cytoplasm	: Red in colour.

Function :

1. Detoxify foreign particles.
2. Collect at the site of allergic reaction.
3. Inhibits antigen-antibody reaction.
4. Important for the dissolution of old clot .
5. Takes part in removing antigen-antibody complex after reaction.

Basophil

Its granules take basic stain .

Character :

i.	Cell size	: 8 - 10 micron
ii.	Nucleus	: Bi- lobed
iii.	Granules	: Coarse , not uniform, & overlap the nucleus.
iv.	Cytoplasm	: Purple blue or blue in colour.

Function :

i. It liberates heparin.
ii. It liberates 5 HT (hydroxytryptamine or sero tonin) and histamine.

Lymphocyte

Definition : Lymphocyte is one of the type of white blood cell. They have no granules.

Formerly, lymphocyte are classified only according to their size. i.e. small, medium or large However it has been shown that there are two main types of immunologically competent lymphocytes.

Character :

i. No granules present.
ii. More cytoplasm.

Cell size: 12-16 micron (*Large lymphocyte*). ***or***

Thin rim of bluish cytoplasm around the nucleus. Cell size : 9-12 micron (*Small lymphocyte*).

iii. Nucleus : Rounded .

iv. Stain : Nucleus - red , Cytoplasm- blue.

Function :

i. Carries antibody formed by reticulo - endothelial system.

ii. They give rise to monocytes, plasma cell, histocytes.

iii. They take part in immune reaction.

iv. They may be converted into firoblast & thus helps in repair of tissue.

v. Delayed hypersensitivity reaction.

Classification of lymphocyte :

A. *According to size :*

1. Small lymphocyte
2. Large lymphocyte

B. *Immunologically :*

1. T-lymphocyte: Responsible for cell- mediated immunity.
2. B-lymphocyte: Responsible for humoral immunity.

(Ref. Wright's 13th Page-57)

B - lymphocyte *(Bursa or bone-marrow processed) :*

Are chiefly involved in the production of humoral immunity in which the plasma cells secretes antibodies against encapsulated pyogenic bacteria (e.g pneumococcus and streptococcus).

T - lymphocyte *(Thymus depended) :*

Are responsible for cell mediated immunity , which is dirrected against intra cellular pathogenic micro-organisms (mainly bacteria, viruses, fungi. and also involved in the rejection of foreign transplants.

Types of T- lymphocyte : There are many different types of T cells. These are classified into three major groups :

i. Helper T cell

ii. Cytotoxic T cell

iii. Suppressor T cell.

Helper T-cell :

The helper T-cells are by far the most numerous of the T cells, usually constituting more than three quarters of all of them. They are so called, as they help in the function of immune system, in many ways. In fact, they serve as the major regulator of virtually all immune functions. They do this by forming a series of protein mediators, called lymphokines, that act on other cells of the immune system as well as on bone marrow cells. Among the important lymphokines secreted by the helper T cells are the following : IL-2, IL-3, IL-4, IL-5, IL-6, GMCS factor, interferon-γ.

(Ref. Guyton & Hall-11th edition; Page 447)

Functions :

The helper T cells form a series of protein mediator called lymphokines that act on other cells of the immune system & on bone marrow. Some of the regulatory functions are-

1. Stimulation of growth & proliferation of Cytotoxic T cells and suppressor T cells.
2. Stimulation of B cell growth & differentiation to form plasma cells and antibodies.
3. Activation of macrophage system.
4. Feed back stimulatory effect on the helper cells themselves.

(Ref. Guyton & Hall-11th edition; Page 447)

Cytotoxic T cell

The cytotoxic T cell is a direct attack cell, capable of killing microorganisms and at times even some of the body's own cells.

The receptor proteins on the surfaces of the cytotoxic cells cause them to bind tightly to those organisms or cells that contain their binding specific antigen.

After binding, the cytotoxic cell sceretes hole-forming proteins, called perforins. Then the cytotoxic cell releases cytotoxic substances directly into the attached cell & kill them.

Functions :

1. They directly attacks the micro-organism & kill them.
2. They also play an important role in destroying cancer cell, heart transplant cells or other types of cells that are foreign to body.

(Ref. Guyton & Hall-11th edition; Page 447)

Suppressor T cells

It is so called because, this cell suppresses the functions of both cytotoxic and helper T cell. It is believed that these suppressor

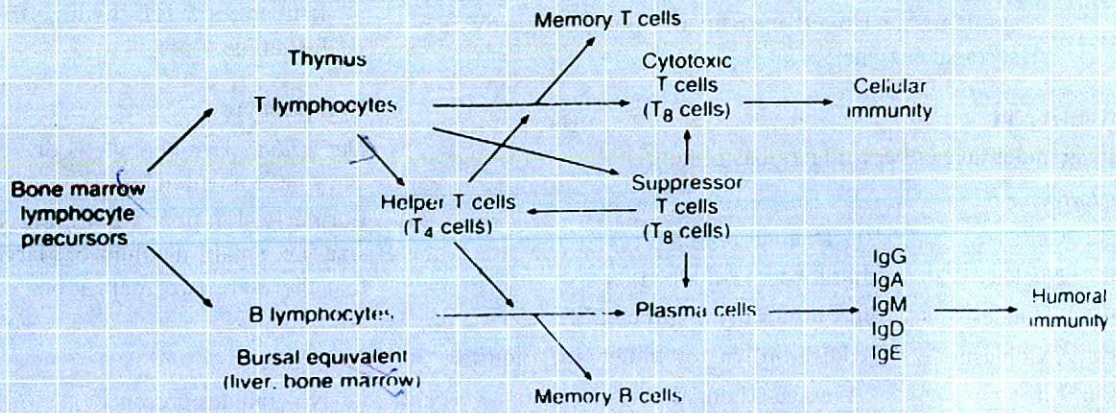


Fig. 5-13. *Development of the system mediating acquired immunity.*

functions serve the purpose of preventing the cytotoxic cells from causing excessive immune reactions that might be damaging to the bodies own response. They are also classified as *regulatory cells*. It is probable that the suppressor T system plays an important role in limiting the ability of the immune system to attack a person's own body tissues, called *immune tolerance*.

(Ref. Guyton & Hall-11th edition; Page 447)

Location of T and B-lymphocyte in adult :

i. *Peripheral blood :* Lymphocytes comprises 60-80 % T cells, 20-30 % B cells.
ii. *Thoracic duct :* Lymphocytes comprises 85-90 % T cells, 10-15 % B cells.
iii. *Lymph nodes :* Contain T cells in the paracortical region and B cells in the subcapsular region, in germinal centres and in medullary cords.
iv. *Spleen :* Contains T cells in periarteriolar sheaths and B cells in germinal centres, red pulp and around periarteriolar sheath.

(Ref. wright's 13th page 57)

Mast cell

Mast cells are heavily granulated wandering cells that are found in areas rich in connective tissue, and they are abundant beneath epithelial surfaces. Their granules contain heparin, histamine, and many proteases. The heparin appears to play a role in granule formation. They have IgE receptors on their cell membranes, and, like basophils, they degranulate when IgE-coated antigens bind to their surface. They are involved in inflammatory responses initiated by immunoglobulins IgE and IgG. The inflammation combats invading parasites. In addition to this involvement in acquired immunity, they release TNF-α in response to bacterial products by an antibody-independent mechanism, thus participating in the nonspecific ***natural immunity*** that combats infections. Marked mast cell degranulation produces clinical manifestations of allergy upto and including anaphylaxis.

(Ref. Ganong 22th Edition, Page-518)

Monocyte

Character :

i. Granules : Absent.
ii. Cell size : 15 - 20 micron.
iii. Nucleus : Kidney shaped .
iv. Cytoplasm : Pale blue in colour .

Function :

These cells are highly phagocytic and remove bacteria and cellular debris.

Monocytes and macrophages : *Monocyte* enter the blood from the bone marrow and circulate for about 72 hours. They then enter the tissues and become ***tissue macrophages***. Their life span in the tissues is unknown, but bone marrow transplantation data in humans suggest that they persist for about 3 months. It appears that they do not reenter the circulation. Some of them end up as the *multinucleated giant cells* seen in chronic inflammatory diseases such as tuberculosis. The tissue ,macrophages include the- *Kupffer cells* of the liver, pulmonary *alveolar macrophages*, and *microglia* in the brain, all of which come from the circulation, in the -past, they have been called the *reticuloendothelial system*, but the general term *tissue macrophage system* seems more appropriate.

The macrophages become activated by lymphokines from T lymphocytes. The activated macrophages migrate in response to chemotactic stimuli and engulf and kill bacteria by processes generally similar to those occurring in neutrophils. They play a key role in immunity. They also secrete up to 100 different substances, including factors that affect lymphocytes and other cells, prostaglandins of the F series, and clot-promoting factors.

(Ref. Ganong 22th Edition, Page-519)

Granulocyte & Macrophage Colony-Stimulating Factors

The production of red and white blood cells is regulated with great precision in healthy individuals, and the production of granulocytes is rapidly and dramatically increased in infections. The proliferation and self-renewal of the pluripotential cells depend on stem cell factor (SCF). Other factors are also involved. The proliferation and maturation of the cells that enter the blood from the marrow are regulated by glycoprotein growth factors or hormones that cause cells in one or more of the committed cell lines to proliferate and mature.

Three additional factors are called colony-stimulating factors (CSFs), because they cause appropriate single stem cells to proliferate in soft agar, forming colonies in this culture medium. The factors stimulating the production of committed stem cells include-

i. Granulocyte-macrophage CSF (GMCSF)
ii. Grarnilocyte CSF (G-CSF)
iii. Macrophage CSF (M-CSF).

Interleukins IL-I and IL-6 followed by IL-3 act in seqqence to convert pluripotential uncommitted stem cdlls to committed progenitor cells. IL-3 is also known as ***multi-CSF***. Each of the CSFs has a predominant action, but all the CSFs and interleukins also have other oveylapping actions. In addition, they activate and sustain mature blood cells. It is interesting in this regard that the genes for many of these factors are located together on the long arm of chromosome 5 and may have originated by duplication of an ancestral gene. It is also interesting that basal hematopoiesis is normal in mice in which the GM-CSF gene is knocked out, indicating that loss of one factor can be compensated for by others. On the other hand, the absence of GM-CSF causes accumulation of surfactant in the lungs.

(Ref. Ganong 22th Edition, Page-519)

Plasma cells

The activated B cells proliferate and transform into memory B cells and plasma cells. The plasma cells secrete large quantities of antibodies into the general circulation. The antibodies circulate in the globin fraction of the plasma and like anti bodies elsewhere, are called immuno globulins. The immuno globins are actually the secreted form of antigen-binding receptors on the B cell membrane.

Immuno globulin are :

a. IgM
b. IgG
c. IgA
d. IgD
e. IgE.

Ig stands for immu noglobulin.

(Ref. Ganong 21th edition)

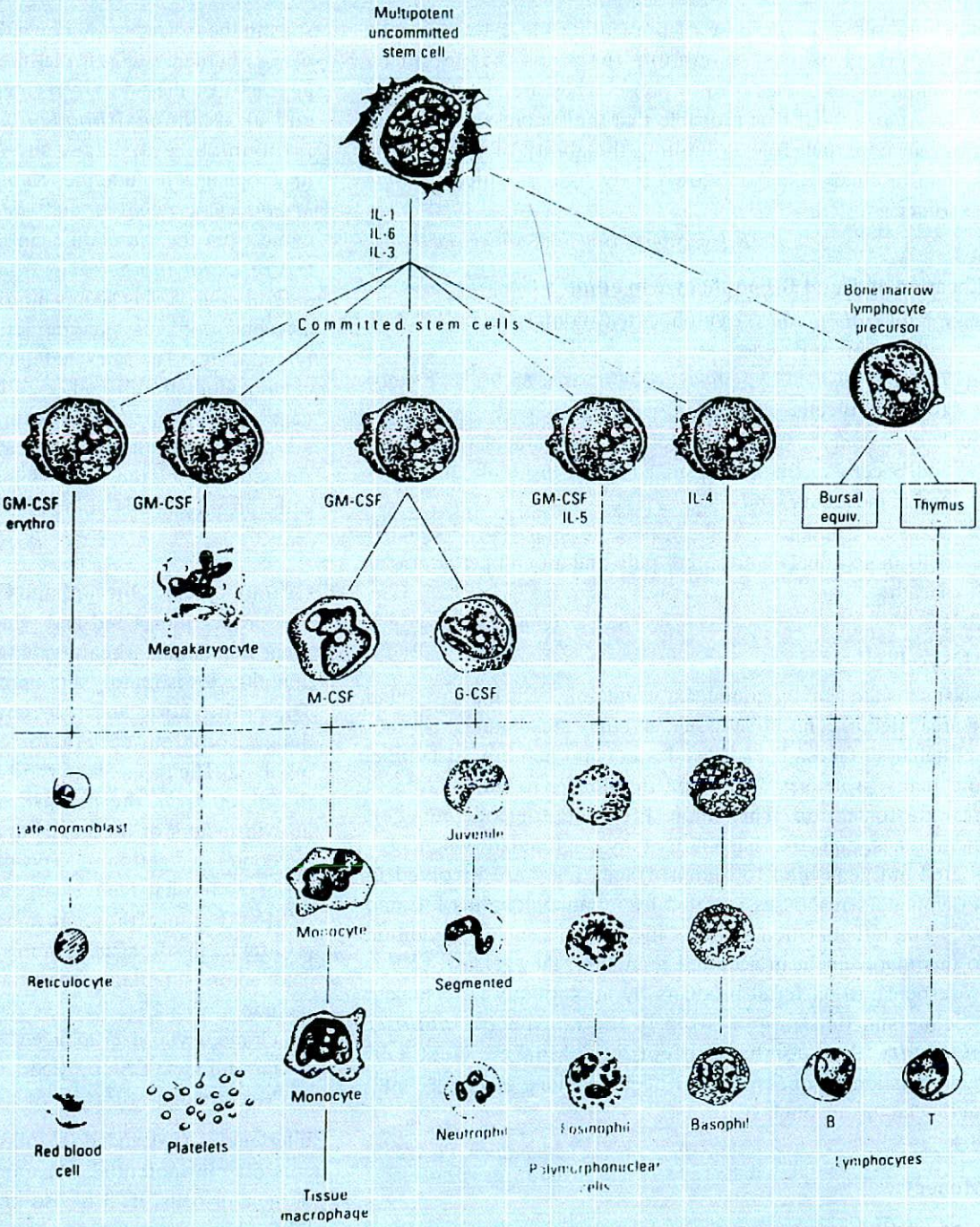


Fig. 5-14. *Development of various formed elements.*

Development of WBC

In the embryo the white corpuscles develop in the mesoderm and migrate secondarily into the blood vessels. In extrauterine life the granulocytes normally develop exclusively in the red marrow ; monocytes and a few lymphocytes also develop from stem cells in the bone marrow and partially in the lymph tissue(lymphocytes and plasma cells). T- lymphocyte matured in the thymus.

Granulopoiesis

The sequence of cells which give rise to the granulocytes in the marrow is as follows :

Pluripotent haemocytoblast

↓

Unipotent commited precursor stem cell

↓

Myeloblast

↓

Promyelocyte

↓

Myelocyte

(Neutrophil, Eosinophil, Basophil)

↓

Causes :

1. Infections :
   a. Bacterial : Typhoid fever
   b. Viral : Infective hepatitis
   c. Protozoal : Kala-azar, Malaria
2. Drug induced leucopcnia
3. Aplastic anaemia
4. Hyperspleenism etc.

Neutrophilia : Increased number of neutrophil above highest normal value of 2700/cu. mm of blood .

Causes:

1. Physiological :
   a. After cxercise
   b. Cold bath
   c. Pregnancy, Perpurium etc.
2. Pathological : Any acute infections. such as acute tonsilitis, pharyngitis, pleuritis, appen-dicitis, nephritis, salphingitis etc.

Neutropenia : Decreased number of neutrophil below lower normal limit of 1500/cu. mm of blood.

Eosinophilia : Increased number of eosinophil above the upper normal limit of 300/cu. mm of blood .

Causes :

1. Allergic disorders- Ashtma, Hay fever etc.
2. Trophical eosinophilia- Wucheriasis.
3. Parasitic infestation - Hook worm
4. Pulmonary eosinophilia-Ascaris lumbri-coides.
5. Malignancy.
6. Familial eosinophilia.

Eosinopenia : Decreased number of eosinophil below the lower normal limit of 150/ cu. mm of blood.

Causes :

1. Electric shock
2. Hormone - ACTH etc.

Basophilia

Increased number of basophil above the upper normal limit of 100/ cu. mm of blood .

Causes : Chronic myeloid leukaemia.

Leukaemia

Definition : The leukaemias are neoplastic disorders of haemopoietic tissue of unknown aetiology characterised by an uncontrolled, abnormal and wide spread proliferation of the leucocytic cells of the body infiltrating the bone marrow and other tissue of the body & usually but not invariably accompanied by the appearance of immature leucocytes in the peripheral blood.

Classification

A. *Depending on the clinical course of the disease :*
   1. Acute leukaemia
   2. Sub-acute leukaemia
   3. Chronic leukaemia.

B. *Depending on the predominant leukaemic cells :*

Acute leukaemia

1. Acute lymphocytic :
   a. Immunological :
      i. Null cell type
      ii. B-cell type
      iii. T-cell type.
   b. Morphological :
      i. Macroblastic
      ii. Microblastic
2. Acute myeloblastic :
   a. Acute granulocytic
   b. Acute pro-Myelocytic
   c. Acute myelomonocytic
3. Acute monocytic
4. Stem cell or undifferentiated type.

Chronic leukaemia :

1. Chronic lymphocytic
2. Chr. monocytic
3. Chr. granulocytic.

Rare subvarieties of acute & chr. leukaemia

1. Erythroleukaemia
2. Eosinophilic leukaemia
3. Megakaryocytic leukaemia
4. Plasma cell leukaemia.

C. *Depending on total WBC in periheral blood :*
   1. Leukaemic leukaemia
   2. Sub-leukaemic leukaemia.

D. ***French-American-Britis (FAB) classification of leukaemia :***
   1. Acute leukaemia :
      a. Acute lymphoblastic leukaemia (ALL) :
         L_1 : Small monomorphic
         L_2 : Large heterogenous
         L_3 : Large homogenous (Barkitt cell type)
      b. Acute myeloblastic leukaemia (AML) :
         M_1 : Myeloblastic (poorly differentiated)
         M_2 : Myeloblastic (well differentiated)
         M_3 : Hypergranular promyelocytic leukaemia
         M_4 : Myelomonocytic leukaemia
         M_5 : Monocytic leukaemia
         M_6 : Erythroleukaemia
   2. Chronic leukaemia :
      a. Chronic granulocytic

↓

Metamyelocyte

(Neutrophil, Eosinophil, Basophil)

↓

Neutrophil Eosinophil Basophil

(Granulocytes)

The cell from the myeloblast stage onwards can be identified in stained bone marrow smears in man. The characteristics of the myeloblast, myelocyte and mature granulocyte are described below :

Myeloblast (12-18 Micro meter diameter) : This cell develops from precursor stem cell; the nucleus is pale, purple blue and round with finely stippled chromatin and several nucleoli. The cytoplasm consists of a narrow blue rim without granules. Protein synthesis is very active as shown by a highly develop endoplasmic reticulum.

Myelocyte (10-15 micro meter diameter) : These cells are characterized by the presence of granules in the cytoplasm. Using Leishman's stain, the myelocyte may be classified according to the colour of the granules into neutrophil (most), eosinophil, and basophil (very scanty). The cytoplasm of the myelocytes as a whole is more extensive and less basophillic, the nucleoli have disappeared and the chromatin is coarser.

Leucocytes : Each type of metamyelocyte gives rise to the correspon ding leucocyte (neutro -phil, eosinophil, baso phil); the nucleus intended then becomes lobed, the granules, in fresh preparation (on a warm stage) instead of motionless, show dancing or streaming movements and the cytoplasm becomes more liquid, so that amoeboid movement occur. The more mature white cells are found lying just external to the sinusoids and pass actively through the intact endothelial lining of these vessels into the circulation.

(Ref. wright's)

Lymphopoiesis

The process of development and maturation of lymphocyte is called lymphopoiesis.

a. *In embryonic stage :* It develops at first from mesoderm. In later part of intrauterine life, the bone marrow also takes part in the lymphocyte formation.

b. *In adult :* The germinal centre of lymphoid tissue is the site of lymphocyte formation. The primitive stem cell is derived from the reticular cell of the lymphoid tissue & its gives rise to lymphoblasts. The mature lymphocytes are developed from the division of lymphoblasts into large lymphocyte and small lymphocyte. Some believe, there is a prolymphocytic stage in between the lymphoblast & large lymphocyte.

Stages of lymphopoiesis :

Reticular cell

↓

Primitive stem cell

↓

Lymphoblast

↓

Prolymphocyte

↓ ↓

Large lymphocyte small lymphocyte.

Leucopoiesis : The process of production of WBC under normal physiological condition is called leucopoiesis .

Granulopoiesis : The process of production of granulocytes under normal physiological condition is called granulopoiesis.

Difference between T & B lymphocyte

T-lymphocyte	*B-lymphocyte.*
1. Thymus dependent	1. Bursa dependent.
2. Concerned with cell mediated immunity.	2. concerned with humoral immunity.
3. Mainly deals with intra cellular bacteria & viruses.	3. Mainly deals with extra cellular bacteria.
4. Release soluble mediators : lymphokines.	4. Produce serum immuno globulins.
5. Constitute 70% of lympho-cytes in peripheral blood.	5. 20% of lymphoc;ytes in the peripheral blood.
6. Present in para-aortic area of a lymphnode.	6. Present in germinal centres of a lymph node.
7. Not inactivated by x-ray radiation.	7. Inactivated.
8. Inactivated by anti lympho-cytic serum.	8. Not inactivated.

Leucocytosis : Increased number of WBC above its upper normal of 11,000/cu mm of blood.

Causes :

A. Physiological :
   i. Emotion, Excercise
   ii. Pregnancy
   iii. Labour
   iv. Purpurium (few days after delivery).

B. Pathological : Any infection such as pyogenic infection, leukemia, malignancy, collagen diseases, tropical eosinophilia.

Leucopenia : Decreased number of WBC below normal limit of 4000/cu. mm of blood .

b. Chronic lymphocytic

3. Unusual type :
   i. Hairy cell
   ii. Polymorphocytic
   iii. Dismyelopoietic syndrome.

Monocyte-Macrophage System

(Reticuloendothelial System)

A large portion of monocytes, however, on entering the tissues and after becoming macrophages, become attached to the tissue and remain attached for month or even for years unless they are called upon to perform specific protective function. They have the same capabilities as the mobile macrophages to phagocytized large quantities of bacteria, viruses, necrotic tissue, or other foreign particles in the tissue and, when appropriately stimulated, they can break away from their attachments and once again become mobile macrophages that respond to chemotaxis and all the other stimuli related to the inflammatory process. Thus the body has a widespread 'monocyte-macrophage system' in virtually all tissue area.

The combination of monocytes, mobile macrophages, fixed tissue macrophages and a few specialized endothelial cells in the bone marrow, spleen and lymph node is collectively called *reticuloendothelial system*. However, all or almost all these cells originate from monocytic stem cells; therefore, the reticuloendothelial system is almost synonymous with the monocyte-macrophage system.

Yet because the term *reticuloendothelial system* is much better known in medical literature than the term *monocyte-macrophage system,* it should be remembered as a generalized phagocytic system located in all tissues but specially in those tissue areas where large quantities of particles, toxins, and unwanted substances must be destroyed.

Tissue macrophages in various tissues differ in appearances because of environmental differences, and they are known by different names ; Kuffer cells-in the liver , reticular cells-in lymph nodes, spleen and bone marrow , alveolar macrophages-in the alveoli of the lungs, tissue histocytes, clasmatocytes or fixed macrophages-in the subcutaneous tissues and microglia - in central nervous system.

(Ref. Guyton & Hall-11th edition; Page 432, 433)

Inflammation

Definition : Inflammation is the localized reaction of vascularized tissue in response to injury involving neurologic, vascular, humoral and cellular changes.

Cause :

Trauma, bacteria and other chemicals and foreign particles, heat or cold, surgery or any other phenomenon may cause inflammation of tissue.

Process of inflammation :

1. Release of vasodilator substances such as histamin, bradykinin, etc, from the injuried tissue.
2. Vasodilation and increase in blood flow to the inflammed area due to the vasodilators is called erythema.
3. Increased permeability of the capillaries with leakage of large quantities of fluid, proteins including fibrinogen into the intercellular spaces causes formation of nonpitting type of oedema.
4. Infiltration of the area by leukocytes.
5. And finally tissue healing by the ingrowth of fibrous tissue.

Purpose of inflammation :

i. To bring the phagocytic cell to the injuried area to engulf the invading agent .
ii. To bring some factors from serum to neutralise the infectious agents.

Cardinal signs of inflammation :

i. Calor : Increase temperature.
ii. Rubor : Redness.
iii. Dolar : Swelling.
iv. Functiolesia : Loss of function.

Principle cytokines

Cytokine	*Cell Lines Stimulated*	*Cytokine Source*
IL-1	Erythrocyte Granulocyte Megakaryocyte Monocyte	Multiple cell types
IL-3	Erythrocyte Granulocyte Megakaryocyte Monocyte	T lymphocytes
IL-4	Basophil	T lymphocytes
IL-5	Eosinophil	T lymphocytes
IL-6	Erythrocyte Granulocyte Megakaryocyte Monocyte	Endothelial cells Fibroblasts Macrophages
IL-11	Erythrocyte Granulocyte Megakaryocyte	Fibroblasts Osteoblasts
Erythro-poietin	Erythrocyte	Kidney Kppffer cells of liver
SCF	Erythrocyte Granulocyte Megakaryocyte Monocyte	Multiple cell types

G-CSF	Granulocyte	Endothelial cells Fibroblasts Monocytes
GM-CSF	Erythrocyte Granulocyte Megakaryocyte	Endothelial cells Fibroblasts Monocytes
M-CSF	Monocyte	Endothelial cells Fibroblasts Monocytes
Thrombo-gdggsa	Megakaryocyte	Liver, kidney.q

L : Interleukin
CSF : Colony stimulating factor
SCF = Stem cell factor.

(Ref. Ganong 22th edition; page-520)

Macrophage and Nutrophil responses during inflammation

1. *Tissue macrophage is the First line of defense against infection* : Within minutes after inflammation those macrophages already present in the tissues, begin their phagocytic action are known as first line of defense.

   These are-

   i. Histocytes in the subcutaneous tissues
   ii. Alveolar macrophages in the lungs
   iii. Microglia in brain etc.

   When activated by the products of inflammation, the first effect is rapid enlargement of each of these cells. Next, break their attachments and become mobile, forming the first line of defense against infection during the first hour or so.

   (Ref. Guyton & Hall-11th edition; Page 434)

2. *Neutrophil invasion of the inflammed area is a second line of defense* : The neutrophils those are present in blood are called second line of defense, because they initiate their action next to tissue macrophages.

   Within the first hour or so after inflammation begins, large number of neutrophils begin to invade the inflamed area from blood and inititate the following reactions-

   i. They alter the inside surface of the capillary endothelium, causing neutrophils to stick to the capillary walls in the inflammed area.
   ii. They cause the endothelial cells of the capillaries and small venules to separate, allowing openings large enough for neutrophils to pass into tissue spaces.
   iii. Other products of the inflammation cause, chemotaxis of the neutrophils towards the injured tissues.

   Thus with in several hours after tissue damage begins, the area becomes well supplied with neutrophils and begin their scavenger functions for removal of foreign matter.

   (Ref. Guyton & Hall-11th edition; Page 435)

3. *A second macrophage invasion into the inflammed tissue is a third line of defense* : Reproduction of already present Macrophages, invasion of monocytes into inflamed area and rapid production & movement of neutrophils into inflamed area are third line of defense.

   The invading monocytes are immature cells requiring 8 hours or more to acquiring the full capacity for phagocytosis.

   (Ref. Guyton & Hall-11th edition; Page 435)

4. *Increased production of granulocytes and monocytes by the bone marrow is a fourth line of defense* : The fourth line of defense is greatly increased productuon of granulocytes and monocytes by the bone marrow. This results from stimulation of the committed granulocytic and monocytic stem cells. However it takes 3 to 4 days before newly formed granulocytes and monocytes reach the stage of leaving the bone marrow. If the stimulus from the inflamed area continues, the bone marrow can continue to produce these cells for months or even for years, sometimes at a rates of production as great as 50 times normal.

   (Ref. Guyton & Hall-11th edition; Page 435)

Immunity

Definition : Human body has the ability to resists almost all types of organism or toxins that tend to damage the tissues and organs. This capacity is called immunity.

Types :

1. *Acquired :* Immunity that develops against individual invading agents such as- bacteria, viruses, toxins and even foreign tissues from other animal. It divides into two types
   a. Humoral immunity or B cell immunity : Body develops circulating antibodies, which are globulin molecules that are capable of attacking the invading agents.
   b. Cell-mediated immunity or T cell immunity : Immunity is achieved throguh the formation of large number of activated lymphocytes that are specifically designed to destroy the foreign agents.
2. *Innate :* Immunity that develops from general processes rather than from process directed at specific disease organisms called innate immunity. It includes -
   a. Phagocytosis of bacteria and other invader by WBC and cells of tissue macrophage system.
   b. Destruction of organism by HCl in stomach and by the digestive enzymes of organism swallowed into the stomach.
   c. Resistance of the skin to invasion by organisms.
   d. Presence in the blood of certain chemical compounds that attatch to foreign organisms or toxins and destroy them such as -
      i. Lysozyme,

ii. Basic polypeptides,
iii. Compliment complex.
iv. Natural killer lymphocytes.

(Ref. Guyton & Hall-11th edition; Page 439)

Antigens

Definition : An antigen is a substance, protein or polysaccharide which when introduced into the system in a considerable dose and appropriate route is capable of inducing an immune response leadihg to formation of antibody with which it reacts specifically.

(Ref: Microbiology M. R. Chowdhury 3rd Page-94)

Haptens : These are the compounds which have lower molecular weights but still can act as antigens. These are called haptens.

After introduction haptens combine with a substance that is antigenic such as serum albumin and form a hapten-protein complex which inturn stimulates the production of an antibody specific aganist haptenic group only, Haptens are-Penicillin, Sulpha, picryl chloride etc.

(Ref. Microbiology M. R.chowdhury)

Criteria of an antigen :

1. It should be macro-molecule. Molecular weight more than $1x10^4$.
2. It shonld be protein or polysaccharide.
3. It should be foreign to the host.
4. It is specific in action.

(Ref. Microbiology M. R.chowdhury)

Antigenic determinants : In an antigenic compound, there are areas or sites which are antigenically active in contrast to other sites which are inactive. These active sites are called antigenic determinants.

(Ref. Microbiology M. R.chowdhury)

Antibody

Difinition : An antibody is a type of globulin (immuno-globulin) produced in response to an antigen with which it reacts specifically.

(Ref. Micro biology- M. R. chowdhury)

Classification of antibody : There are five general types of antibody respectively named-

a. IgM
b. IgG
c. IgA
d. IgD
e. IgE.

Ig stands for immunoglobulin. Of these ***Ig G*** comprises 75% of antibody of normal individuals. ***Ig E*** involved in allergic reaction .

(Ref. Guyton & Hall-11th edition; Page 444)

Structure of an antibody :

Antibody is a Y shaped molecule with a `yoke' and a `shaft'. It has four chains of polypeptide. Two are heavy chains (H) and are known as g, a, m and d in the molecules of IgG, IgA, IgM & IgD respectively. Two are short light chains (L) known as K (Kappa) or l (lamda)

Short light chains enclose heavy chains and all are linked together by disulphide bonds.

Heavy chains are bonded to each other and one short light chain is bound to each of the heavy chain.

There are two antigen combining sites in each molecule situated at the ends of the arms of `y'. There are two regions in each of heavy & short light chain, they are called "Variable portion" and "constant portion" The Variable portion are located near the antigen, combining site and constant portion determines the physical properties of antibody.

(Ref. Microbiology M. R.chowdhury)

Mechanism of action of antibody :

Antibodies act mainly in two different ways-

1. By direct attack on the invader.
2. By activation of the complement system.

Direct action of antibodies on invading agents : The antibodies can inactivate the invading agent in one of several ways, as follows :

1. *Agglutination:* In which multiple large particles with antigens on their surfaces, such as bacteria or red cells, are bound together into a clump.
2. *Precipitation :* In which the molecnlar complex of soluble antigen and antibody becomes so large that it is rendered insoluble and precipitates.
3. *Neutralization :* In which the antibodies cover the toxic sites of the antigenic agent.
4. *Lysis :* In which the antibody directly acts on the membranes of cellular agents and there by causing rupture of the cell.

(Ref. Guyton & Hall-11th edition; Page 444)

Platelets

Definition : Platelet or thrombocyte is one of the formed elements of blood.

Morphology :

i. Diameter : 1-4 µm (or 2-4 µm, *Ganong 21th edition*)
ii. Shape : Oval or rounded.
iii. Nucleus : Absent
(Some granules clamps at the centre of the cell and seems to be a nucleus called false nucleus).
iv. Cytoplasm : Divided into two parts -
   a. Hayalomere : Outer layer, containing granules material consists of microtubules and microfilaments

which contains thrombos thenin, responsible for change of the shape of platelets.

b. Chromatomere : Central deeply stained area, contains alpha granule, glycogen granule, mitochondria, ribosomes, serotonin, endo plasmic reticulum, phospholipid, ATP, ADP etc.

vi. Normal count : 1.5-3.0 lacs/cu. mm of blood. (about 30,000/μL of circulating blood. *(Ganong 22th edition)*

v. Life span : 8 to 12 days (Half life of about 4 days, Ganong).

The platelets in blood are replaced about once every 10 days; in other words, about 30,000 platelets are formed each day for each microliter of blood.

(Ref. Guyton 11th ed; page-457: Ganong 22th edition)

Function

1. *Haemostatic function (Role of platelet in haemostasis)* : It helps in the haemostasis in the following ways :
   a. Vasoconstriction : It liberates 5HT which is a vasoconstrictor.
   b. Formation of platelet plug : It adheres up with collagen tissue and each other and forms plug which prevent bleeding.
   c. Formation of prothrombin activator and help in coagulation : It secretes platelet thromboplastin, phospholipid, ADP which helps in the formation of prothrombin activator and help in coagulation.
   d. Clot retraction : Thrombosthenin of platelet in presence of ADP and Mg^{++} helps in clot retraction.
2. *Initiate blood clotting* : When blood is shed, the platelet disintegrate and liberate thromboplastin which activates prothrombin into thrombin.
3. *Repair capillary endothelium* : While in circulation, the platelet adhere to the damaged endothelial lining of the capillaries and thus bring about a speedy repair.
4. *Helps defensive mechanism* : Due to their increased agglutinating tendencies, they encircle the foreign bodies, thus aids in the defence mechanism of body.

Megakaryocyte

The parent cell of the platelet derived from the reticular cell. Megakaryocyte is a large cell of about 40-150 μm in diameter, polypoid in appearance and containing a large lobulated nucleus out of several nuclei found in the abundant cytoplasm. They are phagocytic and show amoeboid movement. These cell remain out side the vascular sinuses. They through out a part of their cytoplasm like the pseudopodium, through the vessel wall which is shed inside the sinus to form the platelet.

Development of platelets

The parent cell of the platelet is megakaryocyte, derived from reticular cell. They remain out side the vascular sinus. in bone morrow. the megakaryocytes through a part of their cytoplasm. like the pseudopodia, through the wall of the sinosoids. These pseudopodia are broken off in such a way that the individual fragment is surrounded by a unit membrane and are washed away by the blood stream. These fragments with unit membrane are platelet.

Destruction of platelets

Platelets are destroyed by reticuloendothelial cells of spleen & possibly of other places. Platelets contain serotonin, histamin, adrenaline & noradrenaline. They also contain thromboplastin and phosphatidyl-ethanolamine & phosphatidyl serine, needed for coagulation.

Thrombocytosis

Definition : Increased number of Platelet above the upper normal level of 50,000/cu. mm of blood.

Cause :

1. *Physiological :*
   a. Diurnal variation
   b. Exercise
   c. Meal
   d. Convalescence from infections.
2. *Pathological :*
   a. Haemorrhage.
   b. Allergic reaction
   c. Myeloid leukaemia.
   d. After surgical operation.
   e. Hodgkin's disease.

Thrombocytopenia

Decreased number of platelets below the lower normal limit of 2 lacs/ cu. mm of blood.

Haemorrhagic disorders

Classification :

A. ***Haemorrhagic disorders due to vascular defect***

Acquired :

1. Simple easy bruising
2. Senile purpura
3. The symptomatic vascular (non-thrombo cytopenic) purpuras
   a. Infections
   b. Drugs
   c. Uraemia
   d. Cushing's disease & adrenocorticoid administration
   e. Scurvy
   f. Dysproteinaemias
      i. Cryoglobulinaemia
      ii. Benign purpura hyperglobulinaemia
      iii. Macroglobulinaemia
      iv. Multiple myeloma

4. Miscellaneous disorders :
   a. Orthostatic purpuras
   b. Mechanical purpuras
   c. Fat metabolism
   d. Auto-erythrocyte sensitization
   e. Systemic disorders : Collagen diseases, specially polyarteritis nodosa, amyloidosis, allergy.

Congenital :

1. Hereditary haemorrhagic telangiectasia
2. Hereditary capillary fragility
3. Ehlers-Danlos disease.

B. ***Haemorrhagic disorders due to platelet defects*** *(Thrombocytopenia)*

Primary Thrombocytopenia :

1. Acute idiopathic thrombocytopenic purpura
2. Chronic idiopathic thrombocytopenic purpura
3. Cyclical (rare) idiopathic thrombocytopenic purpura.

Secondary thrombocytopenia :

1. Common causes :
   a. Drug & chemicals
   b. Leukaemias
   c. Aplastic anaemia
   d. Malignant lymphomas
   e. Bone marrow infiltration, secondary carcinoma, multiple myeloma, myelosclerosis.
   f. Hypersplenism
   g. D.L.E.
2. Less common causes :
   a. Infection
   b. Megaloblastic macrocytic ana-emia
   c. Liver disease.
   d. Alcoholism
   e. Massive blood transfusion
   f. Defibrination.
3. Rare causes :
   a. Thrombotic thrombocytopenic purpura
   b. Post-partum thrombocytopenia
   c. Post-transfusion thrombocytopenia
   d. Haemangiomas
   e. Food allergy
   f. Idiopathic cryoglobulinaemia

Neonatal and congenital thrombocytopenia :

1. Immune :
   a. Autoimmune : mothers with chronic ITP
   b. Isoimmune : platelet group incompatibility.
2. Infection : Congenital or neonatal
3. Drug adminstration to mother .
4. Congenital megakaryocytic hypoplasia :
   a. Isolated
   b. Associated with congenital abnormalities or pancytopenia.
5. Hereditary :
   a. Sex-linked :
      i. Pure form
      ii. Aldrich's syndrome.
   b. Autosomal dominant or recessive.
6. Congenital leukaemia
7. Giant haemangioma.

C. ***Haemorrhagic disorders due to Coagulation defects***

Congenital coagulation disorders :

1. The haemophilias :
   a. Haemophilia A
   b. Haemophilia B (Christmas disease)
2. Von Willebrand's disease
3. Other congenital deficiency disorders
   a. Fibrinogen deficiency
   b. Prothrombin deficiency
   c. Factor V deficiency
   d. Factor VII deficiency
   c. Factor X deficiency
   f. Factor XI deficiency
   g. Factor XII deficiency (Hageman factor)
   h. Factor XIII (Fibrin stabilizing factor) deficiency
   i. Fletcher factor deficiency.

Acquired coagulation disorders :

1. Vit-K deficiency
2. Liver disease
3. Anticoagulant drugs
4. Acute primary fibrinolysis
5. Disseminated intravascular coagulation (DIC)
6. Massive blood transfusion of stored blood
7. Increased circulating coagulation inihbitors.

Blood Group

Principal Blood Group

1. *ABO System* : Based upon the group specific substances, agglutinogens present in RBC membrane.
2. *Rh System* : Based upon the presence or absence of Rh antigen blood.
3. *M and N system* : Used in determination of paternity.

Classical blood group

ABO system of blood group are calledclassical blood group. Because-

i. It is the principal blood group.
ii. It maintain both 1st and 2nd part of Landstainer's law.
iii. The hazards of mismatched transfusion of ABO system is most effective and appears quickly than others.

Agglutinogens

It is a polysaccharide, present in the cell membrane of R.B.C less commonly in the salivary gland, pancreas, kidney, lungs etc. These are the blood group specific substances. There are thirty different agglutinogens. They appear in 6th week of foetal life and their concentration at birth is about 1/4th of adult. The concentration is maximum at puberty. There are two primary type of agglutinogen, A and B agglutiongen. Specific agglutinogen stimulate the production of specific agglutinin used in the production of immunity.

(Ref. wright's 13th page 47)

Genetic determination of the agglutinogen :

Two genes, one of each of two paired chromosomes, determined the ABO blood groups. These two genes are allelomorphic genes that can be any one of three types but only one type on each chromosome :

1. Type O
2. Type A
3. Type B.

The type O gene is either functionless or almost functionless, so that it causes no significant type O agglutinogen on the cells. On the other hand, type A and type B genes do cause strong agglutinogens on the cells.

The six possible combinations of genes, as shown in table, are OO, OA, OB, AA, BB, and AB. These combinations of genes are known as genotypes, and each person is one of the six genotypes.

Table. *Blood groups with their genotypes and their constituent Agglutinogens and Agglutinins.*

Genotype	*Blood types*	*Agglutinogens*	*Agglutinins*
OO	O	-	Anti-A and Anti-B
OA, AA	A	A	anti-B
OB, BB,	B	B	anti-A
AB	AB	A and B	-

We can observe from the table that a person with genotype OO produces no agglutinogens, and therefore, the blood type is O. A person with genotype OA or AA produces type A agglutinogens and therefore, has blood ype A. Genotypes OB or BB give type B blood and genotype AB gives type AB blood.

(Ref. Guyton & Hall-11th edition; Page 415, 416)

Agglutinin

The agglutinins are gamma globulins, most of them are IgM and IgG are produced in the blood in absence of corresponding agglutinogen in RBC cell membrane. They appears at 10 days after birth and the concentration is maximum at 10th years of age then decline. The two main agglutinins are alpha and beta. Each agglutinogen has its specific agglutinin.

α corresponding to agglutinogen A.

β corresponding to agglutinogen B.

(Ref. Guyton & Hall-11th edition & Wright's)

Q. ***Why agglutinins produced in persons who do not have the antigenic substance?***

Ans : A small quantities of group A and B antigens enter the body in food, in bacteria & in other ways and these substances initiate the development of ati-A or anti-B agglutinins in body.

Importance of blood group study :

i. To know blood group of individuals
ii. Blood transfusion
iii. Certain blood disease
iv. Paternity test (MN system)
v. In foreinsic medicine
vi. Various experimental studies in haematological laboratories.

Agglutination

It may be befined as clumping of red blood corpuscles due to antigen-antibody reaction.

Different group of ABO system

ABO system has 4 sub classes/group : A, B, AB and O.

Group	Agglutinogen (antigen)	Agglutinin (antibody)	Can receive blood from	Can donate to blood group	Percentage among caucasoids
A	A	Beta (β)	A,O	A,AB	41
B	B	Alpha (α)	B,O	B,AB	9
AB	AB	No	A,B,AB	AB	3
O	No	$\alpha\beta$	O	A,B,O	47

(Ref. Guyton & Hall 11th edition)

Group A is again divided into A_1 and A_2. So group AB is again divided into A_1B and A_2B. A_1 includes 75 persent of all group A, A_2 forms 25 percent.

(Ref. Wright's)

Tests done before blood transfusion

i. Group determination by slide method
ii. Cross matching

Determination of blood group *(Slide method)* : Blood is taken from the individual whose blood group is to be determined. It is

diluted 50 times with isotonic saline and thus a suspension of RBC is obtained.

Blood group	*α agglutinin*	*β agglutinin*
A	+	-
B	-	+
AB	+	+
O	-	-

Two seperate drops of suspension are placed on a microscopic slide and test serum containing agglutinin alpha (α) is mixed with one drop and test serum containing agglutinin beta (β) is mixed with other drop.

It is kept for some time and examined under microscope wheather agglutination occured or not. Blood group is obtained from the following data :

Blood group is A	If serum containing agglutinin α agglutinates.
Blood group is B	If serum containing agglutinin β agglutinates.
Blood group is AB	If both agglutinates.
Blood group is O	If none of them agglutinates.

Cross matching

Here the cells of donars blood are directly cross matched with plasma of recepient.

RBC suspension of donar's blood are prepared and mixed with defibrinogenated plasma of recipient. If there is no agglutination, donar and recepient are probably of compitable group and blood transfusion is possible between these two groups.

Difference between cross matching & blood grouping

Cross matching	*Blood grouping*
1. It is the only safe sure guard against transfusion.	1. It can not give such safe guard.
2. In cross matching recipient's serum is directly matched against the donor's RBC.	2. A Known serum (Anti A or anti B) is added to the persons blood.

Landstainer's law

If an agglutinogen is present in the cell membrane of RBC, the corresponding agglutinin must be absent from the plasma i.e in blood group A, agglutinogen A is present in the cell membrane of RBC and the corresponding agglutinin alpha is absent in the plasma.

If there is no agglutinogen in the cell membrane of RBC, the corresponding agglutinin must be present in the plasma i. e. blood group 'O' contain no agglutinogen in RBC membrane and corresponding agglutinin alpha and beta is present in the plasma.

Exception : Landstainer's law is not appreciated for Rh factor as the Rh negative blood contain no agglutinogen in cell membrane and no agglutinin in plasma; similarly absence of M or N substance is not accompanied by the presence of anti-M and anti-N in plasma.

(Ref. Wright's)

Universal Recepient

It is the blood group 'AB' as it can receive moderate amount (200-300 ml) of blood from all the other groups of ABO system.

Let us supose 'B' group is transfused to AB group. 'AB' group contains agglutinogen A and B & 'B' group contains agglutinogen B and agglutinin alpha. But agglutinin alpha present in the plasma of donar is negligible in respect to the agglutinogen A in recepients RBC. So when a moderate amount of blood (200-300ml) is given to AB group, no reaction takes place. But when a large amount of blood is transfused, then some side effects are observed.

Universal Donar

It is the blood group 'O' as it can donate moderate amount of blood (200 - 300ml) to all the other groups of ABO system.

Let us suppose that moderte amount of (200-300ml) group 'O' blood is given to group 'A'. 'A' group contains agglutinogen A in RBC membrane and agglutinin beta in plasma. "O" group contains agglutinin alpha and beta in plasma. But agglutinin alpha present in the donar's plasma is negligible in respect to agglutinogen A present in recepients RBC But when a large amount of blood is transfused, the some side effects are observed. So when a moderate amount of "O" group blood (200 - 300ml) is given to group 'A' no reaction takes place.

The classical terms universal donar and recipient, are however no longer valid as they ignore the complications produced by the existence of the Rh factors.

(Ref. Wright's)

Rh Blood group

It is one of the system of blood group due to the presence or absence of Rh antigen on the cell membrane of RBC. There are several Rh antigens - C, D, E, c, d, e of which D is common. In the Rh system, the agglutinins responsible for causing transfusion reaction almost never occur.

Rh positive blood : Blood with Rh antigen in the cell membrane and Rh antibody (anti-D) absent from theplasma is called Rh positive blood. It is about 85% of all Americans.

Importance : A person with Rh positive blood can receive both Rh positive and Rh negetive blood.

Rh negative blood : Blood group having no Rh antigen in the

RBC cell membrane and corresponding antibody (anti-D) in the plasma is called Rh negative blood. It is about 15% of all Caucasoids and 5% of all Americans.

Causes of development of Rh antibody in Rh negative person :

i. Transfusion of Rh positive blood to Rh negative individual.
ii. Presence of Rh positive foetus in Rh negative mother. It depends upon-
   a. Previous transfusion of Rh positive blood to the Rh negative mother.
   b. Number of pregnancy

Effects of Rh antibody (anti-D) on foetus :

1. Hydrops fetalis.
2. Erythroblastosis fetalis.

Hydrops fetalis : The patient is grossly oedematious; foetus either dies in uterus, or if born prematurely or at term, it dies within a few hours.

Erythroblastosis Fetalis

1. *Definition :* It is a clinical condition characterized by high erythroblast count in foetus.
2. *Cause* : Presence of Rh positive foetus in Rh negative mother. It depends upon-
   a. Previous transfusion of Rh positive blood to the Rh negative mother.
   b. Number of pregnancy.

   Explanation : When Rh positive fetus developed in Rh negative mother, the fetal erythrocyte enter into the maternal circulation during child birth. Then Rh antibody begins to appear in the maternal blood. In second pregnancy if the second fetus is also Rh positive, Rh antibodies (IgG) enter into the fetal circulation. Then agglutination and haemolysis occur (erythroblastosis fetalis).
   i. The infant is developed jaundice at the time of birth or become so within 24 hours.
   ii. There is no anaemia at the time of birth as RBC destruction is more or less compensated by hyperactivity of bone-marrow. But anaemia develops in first few days after birth as the destruction of RBC is maximum after birth.

   If the haemolysis is severe, the following conditions may developed :

   iii. *Kernicterus* : There may be severe neurological lesion involving the basal ganglion and secondarily yellow colouration of them by bile pigments (Kernicterus) due to undeveloped blood brain barrier.
   iv. *Hydrops fetalis* : The patient is grossly oedematious; foetus either dies in uterus, or if born prematurely or at term, it dies within a few hours.
3. Prevention : Anti-D injection is to be given to mother within 72 hours of delivery.
4. *Treament* : Replacement of the newborn infant's blood with Rh negative blood. Approximately 400ml of Rh negative blood is infused over a period of 1.5 or more hours while the baby's own Rh positive blood is being removed after a regular interval during the first weeks of life.

(Ref. Wright's)

Use of stored Blood

Blood transfusion is the ideal treatment for severe haemorrhage when given promptly and in adequate amounts. Modern medical and surgical procedures have greatly increased the number of transfusion; hence it has become necessary to institute blood banks, where blood stored at 4°c is always available.

Ordinarily such blood will be grouped and cross matched, intragroup transfusion being used. If time does not permit the grouping and cross matching of the recepient, Rh- blood should be used. In cases of extreme urgency (war casualties, train accidents) it may be necessary to give O Rh -ve blood, though a proportion of recepient will develop anti-D agglutinins.

(Ref. S. wright's)

Preservation of blood

Red cell undergo rapid changes during storage in simple citrate solution even at 4°C. They are preserved much longer in the presence of glucose.

This acts partly by liberating lactic acid, the resulting fall of pH favouring survival both in vivo and vitro, this effect is usually reinforced by using disodium hydrogen citrate instead of trisodium citrate as an anticoagulant. The cheif effect of glucose, however is to provide substrate for the metabolism, which even at 4°C is still important and contributes to cell survival. During cold storage, reduction of metabolism decreased active transport and cations move with concentration gradient so that cell K^+ fall and plasma K rises from the normal 4-5 mEq/L to 20 or 30 mEq/L in 2 weeks, while cell Na^+ normally about 10 mEq/L rises to 30 or 40 mEq/L.

The change may be sumerized as follows :

1. Increase in cell Na^+, decrease in cell K^+ with a net increase in cell total base and water.
2. As a result the cells swell and become shorter and fatter i.e more spherocytic in consequence they undergo haemolysis more rapidly in hypotonic solution and may rupture in vitro in salt concentrations as high as 0.8 percent.
3. Spontaneous haemolysis of the cells take place to an increasing degree while in contact with their own plasma in the blood bank.
4. The balance of phosphorylation and dephosphorylation is disturbed, phosphoric esters breaking down to liberate inorganic phosphate, which may rise in the cells from 2 to 30 mg per 100 ml, while adenosine triphosphate (ATP)

decreases, the fall expressed as P being from 10 to 20 mg per 100 ml cells. It is probable that the immediate link between glucose and glucolysis on the one hand and cell nutrition and active cation transport on the other is ATP. .

Q. ***Antibody of classical blood group is congenital but antibody of Rh blood group is acquired—Explain.***

Ans. Antibody or agglutinins of classical (ABO) blood group present in the blood in response to the corresponding agglutinogen. That is, blood group A contains- β antibody, group B contains antibody α; group AB contains no antibody and group O contain α, β antibody.

But in the case of individuals whose red cells contain no D agglutinogen, anti-D agglutinins are not naturally present in the plasma, but the production of anti-D is evoked by-

i. Transfusion of a Rh^- individual with Rh^+ blood (experimentally, 0.5ml may sufficient).

ii. By the presence of a Rh^+ fetus in a Rh- mother; in this case the titre of anti-D is not likely to be high, in less the woman has undergone one or more pregnancy.

(Ref. S wright's)

Hazards of mismatched Blood transfusion

The collective changes of the body observed after a mismatched transfusion is called hazards of mismatched transfusion. These are-

A. *Immediate Effect :* Soon after begining the transfusion, perhaps after a few ml of blood have been introduced, the patient complain of violent pain in the back & elsewhere & tightness in the chest. These symptoms are attributed to the agglutinated red cells forming clumps which block capillaries.

B *Delayed Effect :*

1. *Haemolysis of red blood cells :* Occasionally, antibodies are potent enough and composed of the appropriate class of immunoglobulins to cause immediate haemolysis but most frequently the cells agglutinate first and then are mainly entrapped in the peripheral vessels, which then haemolysed.
2. *Post-transfusion jaundice :* Due to the haemolysis of red blood cells concentration of haemoglobin in plasma and tissue spaces rises which is gradually ingested by phagocytic cells and converted into bilirubin. The concentration of bilirubin in the body fluids some times raised high enough to cause jaundice. But if liver function is normal, jaundice usually does not appear unless more than 300 to 500 ml of blood is haemolyzed in less than a day.
3. *Acute kidney shutdown :* It results from three different causes :
   i. The antigen-antibody reaction of transfusion reaction releases toxic substances from the haemolysing blood that cause powerful vasoconstriction.
   ii. The loss of circulating red cells along with production of toxic substances from cells from immune reaction often causes circulatory shock; the aterial blood pressure falls very slow and renal blood flow and urinary output decrease.
   iii. If the total amount of free haemoglobin in the circulating blood is greater than that of quantity which can bind with hepatoglobin; much of the excess leaks through the glomerular membranes into the kidney tubules. If this amount is still slight, it can be reabsorbed through the tubular epithelium into the blood and will cause no harm. But when excess, then the tubular Hb concentration rises and Hb precipitates and blocks many of the tubules; this is specially true if the urine is acidic.

   Thus renal vasoconstriction, circulatory shock and tubular blockage all add together to cause acute renal shut down. If renal shut down is complete, the patient dies within a week to 12 days.
4. Haemoglobinuria: Due to excessive bilirubin production it appears in urine.
5. Reaction due to anti-coagulant.

(Ref. Wright's & Guyton)

Q. *What are the hazards of blood transfusion?*

Ans. Hazards of blood transfusion may be -

a. Febrile reaction.
b. Allergic reaction.
c. Haemolysis.
d. Jaundice.
e. Circulatory overload.
f. Renal failure.
g. Transmission of diseases.
   1. Viral hepatitis
   2. AIDS
   3. Syphilis
   4. Malaria
   5. Other protozoal and bacterial infections.
h. Reaction due to infected blood.
i. Thrombophlebitis.
j. Transfusion haemosiderosis.
k. Complications of massive transfusion.
l. Post transfusion purpura etc.

Coagulation of Blood

Hemostasis

Definition : Hemostasis means prevention of blood loss or arrest of bleeding.

(Ref. Guyton & Hall-11th edition; Page 457)

Mechanism of Hemostasis

Whenever a blood vessel is severed or ruptured, hemostasis is achieved by several different mechanisms, including-

1. Vascular constriction
2. Formation of platelet plug
3. Formation of blood clot as a result of blood coagulation
4. Eventual growth of fibrous tissue into the blood clot to close the hole in the vessel permanently.

(Ref. Guyton & Hall-11th edition; Page 457)

Vascular Constriction : Immediately after a blood vessel is cut or ruptured, the stimulus of the traumatized vessel causes the wall of the vessel to contract; this instantaneously reduces the flow of blood from the vessel rupturd. The contraction results from both nervous reflexes initiated by pain impulses and local myogenic contraction of blood vessel-initiated by direct damage to vascular wall, local humoral factors from the traumatized tissues and blood platelets. The more the vessel that is traumatized, the greater the degree of spasm; this means that a sharply cut blood vessel usually bleeds much more than a blood vessel ruptured by crushing. Vascular spasm last for many minutes or even hours.

(Ref. Guyton & Hall-11th edition; Page 457)

Mechenism of formation of platelet plug : When platelets come in contact with a damaged vascular surface, such as the collagen fibres in the vscular wall or even damaged endothelial cells, they immediately change their characteristics dramastically. They begin to swell; they assume irregular forms with numerous irradiating pseudopods protruding from their surfaces; they become sticky so that they adhere to the collagen in the tissue and to a protein called Von Willebrand factor that spreads throughout the plasma; they secrete large quantities of ADP, and their enzymes form thromboxane A_2. The ADP and thromboxane A, inturn, act on the nearby platelets to activate them as well, and the stickiness of these additional platelets causes them to adhere to the originally activated platelets. Therefore, at the site of any rent in a blood vessel wall, the damaged vascular wall or extravascular tissues elicit activation of successively increased numbers of platelets, thus forming the platelet plug. This is at first a loose plug, but it is usually successful in blocking the blood loss if the vascular opening is small. Then, during the subsequent process of blood coagulation, fibrin threads form. These attach tightly to the platelets, thus constructing an unyielding plug.

(Ref. Guyton & Hall-11th edition; Page 458)

Blood Coagulation

Coagulation : When blood is shed it losses its mobility and converts into semisolid mass due to the conversion of soluble fibrinogen into insoluble fibrin by the action of thrombin. *The process by which the soluble fibrinogen is converted into insoluble fibrin and forms a clot is known as coagulation.*

Causes of coagulation :

i. Trauma to the blood.
ii. Trauma to the tissue.
iii. Contact of blood with collagen fibres in the vascular wall or even damaged endothelial cells.

(Ref. Guyton 11th edition)

Blood coagulation Factors

Cloting factor	*Synonyms*
Fibrinogen	Factor I
Prothrombin	Factor II
Factor III	Tissue thromboplastin (Tissue factor)
Factor IV	Calcium
Factor V	Proacelerin, *labile factor;* Ac- globulin; Ac-G
FactorVII	Serum prothrombin conversion accelerator (SPCA); proconvertin; *stable factor.*
Factor VIII	Antihemophillic factor; AHF; *antihemophillic globulin* (AHG); antihemophillic factor A.
Factor IX	Plasma thromboplastin component; (PTC); *christmas factor*; antihemophil lic factor B
Factor x	Stuart factor; *Stuart-power factor*
Factor xi	*Plasma thromboplastin antecedent ;* (PTA); antihemophillic factor C
Factor xii	Hageman factor
Factor xiii	Fibrin stabilizing factor
Prekallikrein	Fletcher factor
HMWK	High molecular weight kininogen Fitzgerald factor;
Ka	Kallikrein
PL	Platelet phospholipid

(Ref. Ganong 22th edition & Guyton 10th ed; Page-459)

Q. What are the Essential factors for coagulation ? Why they are called essential?

Ans. Essential factors are :

1. Fibrinogen : Factor I
2. Prothrombin : Factor II
3. Tissue factor : Factor III, Tissue thromboplastin
4. Calcium : Factor IV.

They are called essential because due to absence of any one of them coagulation does not occur.

Basic theory of blood coagulation

Over 50 important substances that affect blood coagulation have been found in the blood and tissues, some promoting coagulation, called *procoagulants*, and other inhibiting coagulation, called *anticoagulants*. Whether or not the blood will coagulate depends on the degree of balance between these two groups of substances.

Normally the anticoagulants predominate and the blood does not coagulate; but when a vessel is ruptured, procoagulants in the area of damage become activated and over ride the anti-coagulant, and then a clot does develop.

(Ref. Guyton & Hall-11th edition; Page 459)

General mechanism of blood coagulation

(Stages of blood coagulation):

1. First : A complex of substances called prothrombin activator is formed in response to rupture of the vessel or damage to the blood itself.
2. Second : The prothrombin activator catalyzes the conversion of prothrombin into thrombin.
3. Third : The thrombin acts as an enzyme to convert fibrinogen into fibrin threads that enmesh platelets, blood cells, and plasma to form the clot itself.

(Ref. Guyton & Hall-11th edition; Page 459)

Formation of Prothrombin Activator

Prothrombin activator is formed in two basic ways-

a. By the extrinsic pathway that begin with trauma to the vascular wall and surrounding tissues.

b. By the intrinsic pathway that begin in the blood itself.

Extrinsic mechanism : The extrinsic mechanism for initiating the formation of prothrombin activator begin with blood coming in contact with traumatized vascular wall or extravacular tissues and occurs according to the following three basic steps.

1. *Release of tissue factor (or tissue thromboplastin) :* Traumatized tissue releases a complex of several factors called tissue factor or tissue thromboplastin. This includes specially *phospholipids* from the membranes of the tissue plus a *lipoprotein complex*, that functions mainly as a *proteolytic enzyme*.
2. *Activation of factor X - role of factor VII and tissue factor :* The lipoprotein complexe of tissue factor further complexes with blood coagulation factor VII, and in the presence of calcium ions, acts enzymatically on factor X to form activated factor X (Xa).
3. *Effect of activated factor X (Xa) to form prothrombin activator- role of factor V :* The activated factor X combines immediately with tissue phospholipids that are part of tissue factor or with additional phospholipids released from platelets as well as with factor V to form the complex called prothrombin activator.

(Within a few seconds, in the presence of calcium ions, this splits prothrombin to form thrombin. Then thrombin acts as an enzyme to convert fibrinogen into fibrin threads that enmesh platelets, blood cells, and plasma to form the clot itself.)

(Ref. Guyton & Hall-11th edition; Page 461, 462)

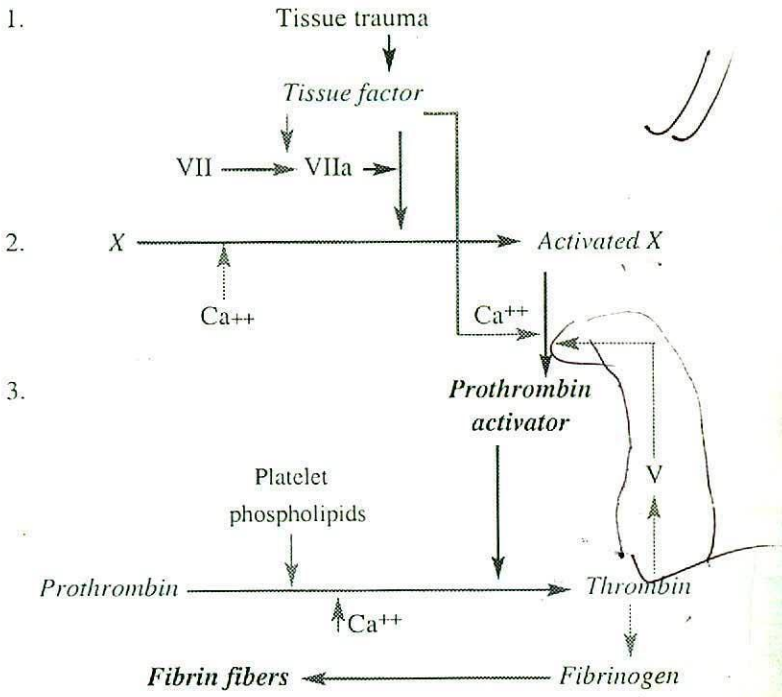


Fig. 5-16. *The extrinsic pathway for initiating blood coagulation.*

(Ref. Guyton & Hall-11th edition; Page 461)

Intrinsic mechanism : It begins with trauma to the blood itself or exposure of the blood to collagen from a traumatized blood vessel wall and continues through the following series of cascading reactions.

1. *Activation of factor XII and release of platelet phospholipids by blood trauma :* Trauma to the blood or exposure of the blood to collagen from a traumatized blood vessel wall alters two important clotting factors in the blood: factor XII and the platelets. When factor XII coming into contact with collagen or with a wetable surface such as glass (particularly a negatively charged surfac), it takes on a new configuration that converts it into a proteolytic enzyme called *activated factor XII*. Blood trauma also damages the platelets and this releases plateles phospholipid which also plays a role in subsequent clotting reactions.
2. *Activation of factor XI :* The activated factor XII acts enzymatically on factors XI to activates this factor as well. This reaction also requires *HMW kininogen*, and is accelerated by *prekallikrein*.

3. *Activation of factor IX by activated factor XI :* The activated factor XI acts enzymatically on factor IX in presence of Ca^{++} and converts it into activated factor IX.

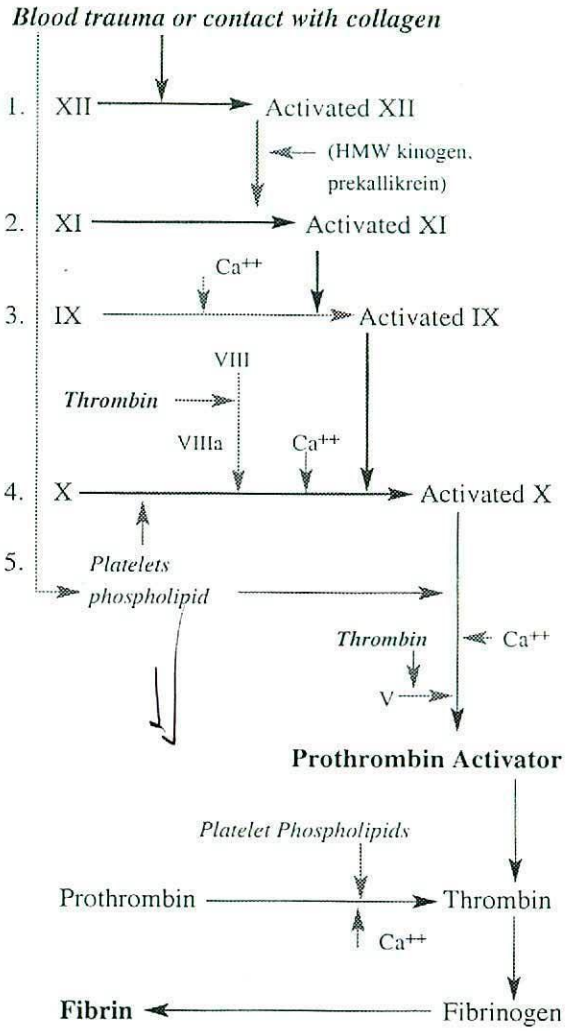


Fig. 5 - 17. *The intrinsic pathway for initiating blood coagulation.*

4. *Activation of factor X -role of factor VIII :* The activated factor IX, acting in concert with factor VIII and with platelets phospholipids and factor 3 from traumatized platelets, activates factor X.

5. *Activation of activated factor X to form prothrombin activator- role of factor V :* Activated factor X combines with factor V and platelet or tissue phospholipids to form the complex called prothrombin activator.

(Within a few seconds, in the presence of calcium ions, this splits prothrombin to form thrombin. Then thrombin acts as an enzyme to convert fibrinogen into fibrin threads that enmesh platelets, blood cells, and plasma to form the clot itself.)

(Ref. Guyton & Hall-11th edition; Page 462, 463)

Convertion of prothrombin to thrombin

Prothrombin is converted into thrombin under the influence of prothrombin activator and calcium ions.



The rate of formation of thrombin from prothrombin is almost directly proportional to the quantity of prothrombin activator available, which itself is approximately prortional to the degree of trauma to the vessel wall or to the blood.

(Ref. Guyton & Hall-11th edition; Page 459)

Conversion of Fibrinogen to Fibrin *(Formation of clot)*

Thrombin acts on fibrinogen to remove four low molecular weight peptides from each molecule of fibrinogen, forming a molecule of fibrin monomer that has the automatic capability of polymerizing with other fibrin monomer molecules. Therefore many fibrin monomer molecules polymerize within second into long fibrin threads that form the reticulum of the clot. In early stages of polymerization, the fibrin monomer molecules are held together by weak non-covalent bonds and the threads also are not cross linked with each other. But when fibrin stabilizing factor is activated, operates as an enzyme to cause covalent bonds between fibrin monomer molecules as well as multiple cross-linkages between the adjacent fibrin threads, thus adding tremendously to the three dimentional strength of the fibrin mesh work (clot).

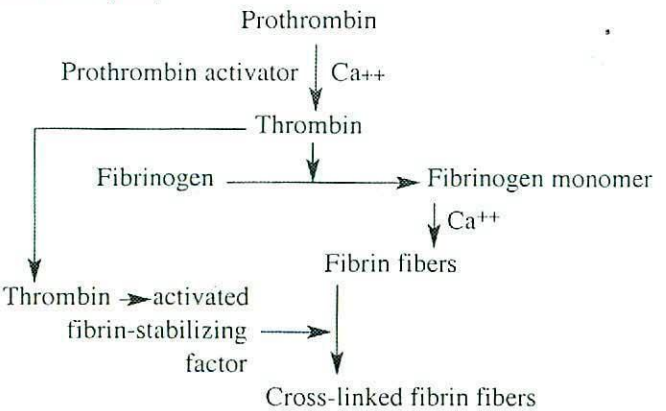


Fig. 5-18. *Schema for conversion of prothrombin to thrombin and polymerization of fibrinogen to form fibrin fibers.*

(Ref. Guyton & Hall-11th edition; Page 460)

Seeger's concept of blood coagulation :

Prothrombin is converted into prethrombin and auto-prothrombin III. Autoprothrombin III then converted into autoprothrombin C & peptides in presence of calcium ions, tissue extract & platelet co-factor 1. Autoprothrombin C then acts upon prethrombin and form thrombin. This process is

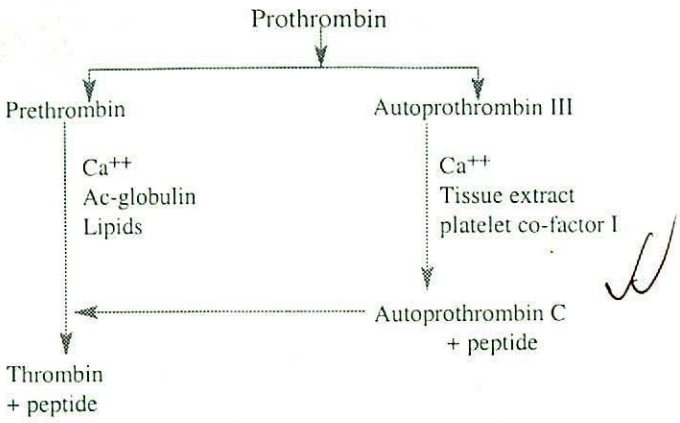


Table. *Seeger's concept of blood coagulation* *(Ref. S. Wright's)*

known as Seeger's concept of blood coagulation.

(Ref. S. Wright's)

Defference between extrinsic And intrinsic mechanism of coagulation.

Extrinsic mechanism	*Intrinsic mechanism*
1. It occurs due to trauma to tissue.	1. It occurs due to trauma to blood itself or contact with collagen.
2. It is explosive in nature to produce prothrombin activator.	2. It is much slower.
3. Tissue phospholipid acts in this pathway.	3. Platelets phospholipid acts in this pathway.
4. It begins with the activation of factor X and requires factor VII, V & Ca^{++}	4. It begins with the activation of factor XII & requires factor XI, IX, VIII, X & V and Ca^{++}.
5. Thrombin is not required in this pathway.	5. Thrombin is required.
6. In it, the composition of prothrombin activator is tissue phospholipid, factor X, V, and Ca++.	6. In it, the composition of prothrombin activator is platelet phospholipid, factor X, Vand Ca++.

Clot

Definition : When blood is shed, it converts into a semisolid mass due to conversion of soluble fibrinogen into insoluble fibrin thread. This solid mass is called clot. The clot is composed of a meshwark of fibrin threads running in all dirrection & entrapping blood cells, platelets and plasma.

Blood does not clot inside the blood vessel due to-

1. *Endothelial surface factor :*
   a. Smoothness of the endothelium prevents contact activation of the intrinsic clotting system i.e. prevents the initiation of the formation of the prothrombin activator.
   b. Presence of monomolecular layer of protein adsorbed to the inner surface of the endothelium that repel the platelets and clotting factors, thereby preventing activation of clotting.
2. *Speed of the blood flow :* It prevents the intravascular coagulation.
3. *Presence of natural anti-coagulant :*
   a. *Heparin :* Secreted by mast cells or basophil, prevents coagulation.
   b. *Antithrombin :* It removes the thrombin from blood as a result fibringogen can not be converted into fibrin.
   c. *Fibrin :* Fibrin thread itself absorbs thrombin.
   d. Absence of coagulation factor III or thromboplastin.

Q. ***What is clot retraction?***

Ans.

Within a few minutes after a clot is formed, it begins to contract and losses most of its fluid within 30 to 60 minutes and reduced in size. This is called clot retraction. The fluid that comes out after clot retraction is called serum which is straw in colour.

Q. ***Name the different anti-coagulant and their mode of action.***

Ans.

1. *Natural anti-coagulant :*
   a. Heparin: Blood level .01 mg/100ml of blood.
      i. By itself, heparin has little or no anticoagulant property, but it combines with antithrombin III and removes thrombin from blood and thus to acts as an anti-coagulant.
      ii. The complex of heparin and anti-thrombin III also removes several other activated factor from blood such as factor XII, XI, IX and X. Thus enhancing the efectiveness of anti-coagulant.
   b. Antithrombin : It removes the thrombin form blood.
   c. Fibrin : Fibrin threads itself absorbs thrombin.
   d. Anti-thromboplastin.
2. *Artificial anti-coagulant :*
   a. Heparin : It also can be prepared artificially.
   b. Sodium citrate or oxalate: By precipitating Ca^{++} from blood as calcium citrate or oxalate.
   c. EDTA (Ethylenediamine-tetraacetate) : Acts by removing ionic Ca^{++} from blood.
   d. Phenindione.

(Ref. Guyton & Hall-11th edition & others)

Q *What is haemorrhage? what are the causes of haemorrhagic state ?*

Ans. Haemorrhage is the abnormal internal or external discharge of blood. May be arterial, venous or capillary from blood vesssels into tissues, into or from the body.

Effect of haemorrhage : Decrease Blood volume → Decrease of venous return → Decrease of cardiac output → Decrease of blood pressure.

The clinical haemorrhagic states are due to

1. Defect in blood clotting or coagulation disorder :
   a. Fibrinogenopenia: Due to lack of fibringogen, coagulation time quick and prothrombin time prolongs.
   b. Hypoprothrombinaemia: Dimination of prothrombin formation due to lack of Vitamin K which helps in the synthesis of it. Prothrombin time is prolonged.
   c. Haemophilia : Due to lack of factor VIII, coagulation time abnormally prolongs here.
2. Defect due to vascular system or capillary contraction.
3. Defect due to deficiency of platelets.
4. The combined defect.

Examples of diseases due to deficiency of clotting factors.

Deficiency of Factor :	*Clinical Syndrome*	*Cause*
Factor i.	Afibrinogenesis	Depletion during pregnancy with mature separation of placenta; also congenital (rare).
Factor ii.	Hypoprothrom-binemia (hemorr-hagic tendency in liver disease	Decreased hepatic synthesis, usually secondary to vitamin K deficiency.
Factor v.	Parahemophilia	Congenital
Factor vii.	Hypoconvertivemia	Congenital
Factor viii.	Hemophilia A (classic hemophilia)	Congenital defect due to various abnormalities of the gene of X chromosome that codes for factor VIII; diseases is therefore inherited as sex linked characteristic.
Factor ix.	Hemophilia B (Christmas disease)	Congenital
Factor x.	Sturt-Prower factor deficiency	Congenital
Factor xi.	PTA deficiency	Congenital
Factor xii.	Hageman trait	Congenital

Difference between haemostasis and coagulation

Haemostasis	*Coagulation*
1. Haemostasis means prevention of blood loss or arrest of bleeding.	1. Coagulation is the process by which fibrinogon is converted into fibrin thread and forms a clot.
2. Haemostasis is achieved by the vascular spasm, platelet plug formation.	2. Coagulations begins with the formations of prothrombin activator.
3. Haemostasis occurs through 4 steps.	3. Coagulation is one of the steps of haemostasis.
4. Platelet is essential for haemostasis.	4. Platelet is not essential for coagulation (e.g extrinsisc pathway).

Q. *What is fibrinloysis? What is its singnificance?*

Definition : It is the process by which fibrin threads are liquified or dissolved by profibrinolysin. The profibrinolysin is converted into fibrinolysin by means of an activating enzyme present in the tissue serum, urine and some bacteria. The fibrinolysin then disintegrates the fibrin network and dissolves the clot into soluble peptide. But it also acts upon prothrombin and factor VIII, V and XII etc.

Significance :

i. Allows clearing of blood vessels.
ii. Re-open the cloted blood vessel
iii. Remove very minute clots from peripheral vessels.

Haemophilia

Definition : It is a sex linked disease transmitted by females who themselves show no symptom, to male who manifests signs of the disease. It is characterized by abnormally problonged coagulation time but the bleeding time is normal.

Types :

1. Haemophilia A : Due to deficiency of factor VIII (85%).
2. Haemophilia B : Due to deficiency of factor IX (15%).

Effects : Joint become severely damaged because of repeated haemorrhage during exercise or after injury.

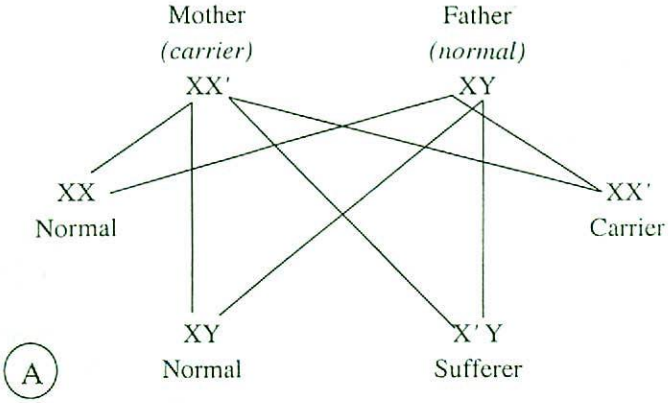
Q. *Why factor VIII is called anti-hemophillic factor?*

Ans. When either factor VIII or platelets are short in supply, activation of factor X into active factor X is deficient. Factor VIII is the factor that is missing in the person who has classic hemophilia, for which reason factor VIII is called anti hemophillic factor.

Q. *Female is carrier but not sufferer-why?*

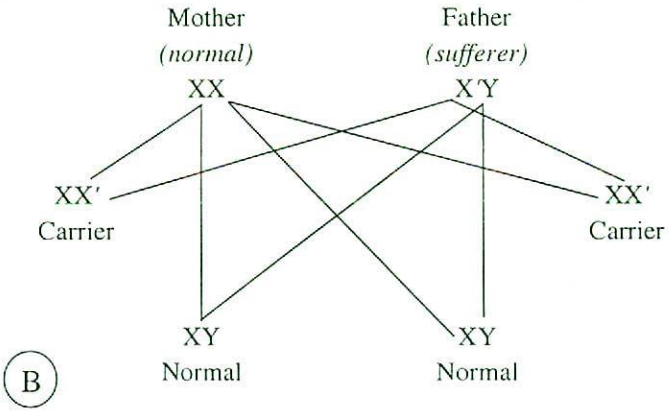
Ans. Haemophilia occurs due to deficiency of factor viii and ix. Both these factors are transmitted genetically by way of the

female chromosome as a recessive trait.



(A)

Therefore, almost never will a woman have hemophilia because at least one of her two X chromosomes will have the



(B)

appropriate genes. However, if one of her X chromosomes is deficient, she will be a haemophilia carrier, transmitting the disease to half her male offspring and transmitting the carrier state to half her female offspring.

(Ref. Guyton & Hall-11th edition; Page 465)

Purpura

It is a clinical condition characterized by a tendency of spontaneous haemorhage beneath the skin and mucous membrane from the various internal organs. It is due to platelet deficiency or vascular defects. Here coagulation time is normal but bleeding time is prolonged.

It is of two types :

1. *Thrombocytopenic purpura :* Due to low platelet count. Skin displays small purplish pteeches.
2. *Thrombosthenic purpura :* Platelet count normal but capillary are tortous and abnormal.

Difference Between Hemophilia and purpura

Hemophilia	*Purpura*
1. Inherited sex linked anomaly, transmitted by female to male who manifestes the sign.	1. It is a clinical condition characterised by a tendency of spontaneous haemorrhage beneath the skin and mucous membrane from the various internal organs.
2. Here coagulation time is prolonged, bleeding time is normal.	2. Here coagulation time is normal but bleeding time prolonged.
3. It is due to deficiency of factor VIII, IX and XI	3. It is due to platelet deficiency or capillary factor.
4. It is inherited, only shown in male.	4. It is not inherited, manifested by both male and female.

Bleeding time

Definition : Bleeding means extravastion of blood i.e. a process of coming out of blood from the vasculature. Bleeding time is the time required for the stopage of bleeding.

Normal bleeding time is 1 to 6 minutes. However, the time depends largely on the depth of the wound and other degree of hyperemia in the finger at the time of the test. Lack of several of the clotting factors can prolong the bleeding time but this is specially prolonged by lack of platelets.

Method of determination of bleeding time :

There are two methods :

1. *Duke's method :*
   i. After all antiseptic precautions prick the finger tip. Start the stop-watch when blood starts oozing out.
   ii. With a round blotting paper, touch the bleeding point at an 15 seconds interval, until bleeding stops. The time difference will give the bleeding time.
2. *Ivy's method :*
   i. Inflate the cuff of the sphygmomanometer over the elbow joint and keep at the preseure of 10 mm of Hg till the end of the test.
   ii. Taking all the antiseptic precautions, prick the skin with a needle at two places, 5-10 cm apart on the anterior surface of the forearm.
   iii. Repeat the second step of Duke's method.

Normal value :

i. Ivy's method : upto 11 min.
ii. Duke's method : upto 8 min.

Clotting time

i. *Definition :* Time required for coagulation of blood.
ii. *Normal clotting time :* It is about 6 to 10 minutes.
iii. *Normal clotting time is prlonged due to-*
   a. Haemophilia
   b. Deficiency of any of the factors in the intrinsie pathway for clotting

Measurement : *Methods of determination of clotting time :*
Following two methods are commonly used :

1. ***Lee and white method*** (Whole blood coagulation time) :
   i. Arrange four small test tubes which are previously warmed to 37°C.
   ii. Draw 5 ml. blood from antecubital vein. Start the stop-watch as soon as the blood enters the syringe.
   iii. Transfer one ml. of blood into each of the four test tubes.
   iv. Tilt each test tube after an interval of 30 seconds.
   v. Stop the stop-watch immediately when the blood does not spil out, even when the tube is tilted upto 90° angle.
   vi. Note the time period for the four tubes and the average of them will give the coagulation time.
2. ***Capillary tube method*** :
   i. After taking all antiseptic precautions, prick the finger or the ear lobe. Start the stop-watch when blood starts oozing out.
   ii. Wipe out the first drop of blood. By touching the tip to the blood drop, fill the capillary tube.
   iii. Break the capillary tube upto half an inch length, each time at an interval of thirty seconds.
   iv. Stop the watch at the point when fibrin thread appears from the side of the broken tubes. Note the time which will give the coagulation time.

Normal value :
i. 5 to 11 min in lee and white method.
ii. 2 to 4 min in capillary tube method.

Prthrombin time
i. *Definition* : The time required for coagulation to take place is known as the prothrombin time.
ii. *Normal value:* Approximately 12 seconds.
iii. *Importance* : rothrombin time gives an indication of the total quantity of prothormbin in the blood & also the quantities of other clotting factors in the body.

(Ref. Guyton 11th edition)

Bone Marrow

In the adult, red blood cells, many white blood cells, and platelets are formed in the bone marrow. In the fetus, blood cells are also formed in the liver and spleen, and in adults such extramedullary hematopoiesis may occur in diseases in which the bone marrow becomes destroyed or fibrosed. In children, blood cells are actively produced in the marrow cavities of the bones. By age 20, the marrow in the cavites of the long bones, except for the upper humerus and femur, has become inactive. Active cellular marrow is called red marrow; inactive marrow that is infiltrated with fat is called yellow marrow.

The bone marrow is actually one of the largest organs in the body, approaching the size and weight of the liver. It is also one of the most active. Normally 75% of the cells in the marrow belong ot the white blood cell-producing myeloid series and only 25% are maturing red cells, even though there are over 500 times as many red cells in the circulation as there are white cells. The difference in the marrow reflects the fact that average life span of white cells is short whereas that of red cells is long.

The bone marrow contains mulipotent uncommited stem cells (pluripotential stem cells) that differentiate into one or another type of committed stem cells (progenitor cells). These in turn differentiate into the various differentiated types of blood cells. There is now evidence that there are pluripotential stem cells and progenitor cells in the blood as well. The pluripotential cells few in number but are capable of completely replacing the bone marrow when injected into a host whose own bone marrow has been completely destroyed.

There are separate pools of progenitor cells for megakaryocytes, lymphocytes, erythrocytes, eosinophils, and basophils, whereas neutrophils and monocytes arise from a common precursor. The bone marrow stem cells are also the source of osteoclasts, Kupffer cells, mast cells, dentritic cells, and Langerhans cells.

Some important biochemical & haematological normal values

Venous Blood : Approx. Adult Reference values

Analysis	*Reference values*	
	S.I. Units	*Others units*
Acid phosphatase		0.1-0.4 u/1
Alanine aminotransferase (ALT)		10-40 u/1
(glutamic-pyruvic transaminase -GPT)		
Alkaline phosphatase		40-100 u/1
Asparatate Aminotransferase (AST)		10-35 u/1
(glutamic-oxaloacetic transaminase (GOT)		
Bilirubin (toal)	2–17 micro mol/1	0.3-1.0 mg/dl
Calcium (total)	2.12–2.62 mmol/1	8.5-10.5 mg/dl
Carbon dioxide (Total)	24–30 mmol/1	
Cholesterol (fasting)	3.6–6.7 mmol/1	145-270 mg/dl
Creatinine	55–150 micro mol/1	0.6-1.7 mg/dl
a–Fetoprotein	2–6 units/ml	< 30 mg/ml
Gulcose (fasting)	< 5.5 mmol/1	100 mg/dl
D–Glutamyl transferase		male— 10-55 unit/L
		female— 5-35 unit/L
Immunoglobulins (Ig) IgA	0.5–4.0 g/1 (40–300 i.u./1)	
IgG	5.0–13.0 g/1 (60–160 i.u./1)	
IgM-males	0.3–2.2 g/1 (40–270 i.u./1)	
females—	0.4–2.5 g/1 (50-300 i.u./1)	
Iron—males	14–32 micro mol/1	77-178 micro g/dl
females	10–28 micro mol/1	56-156 micro g/dl
Iron binding capacity (total)	45–72 micro mol/1	250-400 micro g/dl
Iron binding capacity (saturation)		14-47%
Lactate	0.4–1.4 mmol/1	3.6-13.0 mg/dl
Lactate dehydrogenase (LD)		100-300 u/l
Potassium	3.3-4.7 mmol/1	
Sodium	132-144 mmol/1	
Proteins—total	62-82 g/1	6.2-8.2 g/dl
Albumin	36-52 g/1	3.6-5.2 g/dl
Globulins	24-37 g/1	2.4-3.7 g/dl
Urea	2.5-6.6 mmol/1	15-40 mg/dl
Vitamin A	0.7-17 micro mol/1	20-50 micro g/dl

Arterial blood analysis :

Analysis	*Reference values*	
	S.I. units	*Other units*
Ammonia	11-35 micro mol per 1	20-63 micro g per dl
Hydrogen ion	36-44 n mol per 1	PH 7.37-7.45
Carbon dioxide ($PaCO^2$)	4.8-6.0 kPa	36-45 mm Hg
Plasma bicarbonate	21-27.5 mmol per 1	21-27.5 m Eq per L
Oxygen (PaO^2)	11-13 kPa	83-98 mm Hg
Cerebrospinal fluid		Gastrointestinal
(Lumber puncture)		Faecal fat : < 18 mmol per 24 h
Cells : 5/mm3 (all lymphocytes)		(< 5g per 24 h)
Glucose :	2.5-4.0 mmol per L (45-72 mg/dl)	Stool wt : < 200 g per 24 h
	50 to 70% of plasma concentration.	Liver
		Copper : < 50 micro g per g dry weight
Immunoglobulin G :	20-50 mg per 1	
Protein (total) :	100-400 mg per 1	(Wilson's disease > 250 micro g per g dry weight).
Pressure :	5-15 cm C.S.F.	

Haematological values

	S.I. Units	Other Units
Bleeding time	Up to II min	
Body fluid (total)		50% (obese) — 70% (lean) of body wt.
Intracellular		30-40% of body wt.
Extracellular		20-30 of body wt.
Blood volume		
Red cell mass—men	30 ± 5 ml per kg	
Women	25 ± 5 ml per kg	
Plasma volume (both sexes)	45 ± 5 ml per kg	
Total blood vol, men	75 ± 10 ml per kg	
women	70 ± 10 ml per kg	
E.S.R. (westergren)	0—6 mm in 1 h-normal	
(Figures given are for pts	7-20 mm in 1 h-doubtful	
under 60 yrs of age)	> 20 mm in 1 h-abnormal	
Fibrinogen	1.5-4.0 g per 1	150–400 mg per dl
Folate— Serum	2-20 micro g per 1	2-20 ng per ml
— red cell	> 100 micro g per 1	> 100 ng per ml.
Haemoglobin— men	13-18 g per dl	13-18 g per 100 ml
— women	11.5-16.5 g per dl	11.5-16.5 g per 100 ml
Haptoglobin	0.3-2.0 g per 1	30-200 mg per dl
Leucocytes—adults	4.0-11.0 x 10^9 per 1	4000-11000 per micro 1
D.C. (W.B.C.)		4.0-11.0 x 10^3 per m3
Neutrophil	2.5-7.5X10^9 per 1	40-75%
Lymphocytes	1.0-3.5 x 10^9 per 1	20-40%
Monocytes	0.2-0.8 x 10^9 per 1	2-10%
Eosinophil	0.04-0.4 x 10^9 per 1	1-6%
Basophil	0.01-0.1 x 10^9 per 1	0-1%
MCH	27-32 pg	27-32 micro micro g
MCHC	30-35g per dl	30-35%
MCV	78-98 fl	78-98 micro3 or micro m3
PVC or haematocrit—men	0.40-0.54	40-54%
women	0.35-0.47	35-47%
Platelets	150-400 x 10^9 per 1	15000-400000 per micro 1 or mm3
Prothromibin time	11-15s	
Red cell count—men	4.5-6.5 x 10^{12} per 1	4.5-6.5 x 10^6 per micro 1 or mm.
—women	3.8-5.8 x 10^{12} per 1	3.8-5.8 x 10^6 per micro 1 or mm.
Red cell life span (mean)	120 d	0.2-2%
Reticulocytes (adults)	10-100 x 10^9 per 1	160-925 pg per ml or micro micro g per ml.
Vit B12 (serum cyanocobalamin)	160-925 ng per 1	

(From Davidson's Medicine, 16 th edition)

Introduction 5.49 | *Hemoglobin 5.51* | *Anaemia 5.53* | *Immunity 5.55* | *Blood group 5.57*
Serum/Plasma 5.50 | *ESR 5.52* | *Jaundice 5.54* | *Inflammation 5.56* | *Coagulation of blood 5.58 -5.61*
Red Blood Cell 5.50 | *Iron & Fate of RBC 5.52* | *White Blood Cell 5.54* | *Platelet 5.57*

Directions : *Write T for true & F for false against each of the following statement.*

Introduction

Q.01. **Blood**
- T a. is responsible for 8% of the total body weight.
- T b. acts as a buffer.
- T c. is a modified connective tissue.
- F d. pH ranges from 7.2 to 7.6.
- F e. volume decrease in polyeythemia.

Q.02. **Blood volume is**
- T a. 70 ml/kg body weight.
- T b. about 8% of the total body weight.
- T c. calculated by dye dilution method.
- T d. decreased after haemorrhage.
- F e. increased in severe dehydration.

Q.03. **Specific gravity of blood**
- T a. rapidly falls after birth.
- T b. is 1056
- T c. depends on its plasma protein contents
- F d. of foetal blood at full term is lowest.
- F e. is decreased in dehydration.

Q.04. **Packed cell volume is**
- T a. increased in bone marrow hyperplasia.
- T b. measured by centrifugation of blood.
- T c. determined by wintrobe method.
- T d. increased after fluid loss.
- F e. decreased in polycythemia.

Q.05. **Nitrogenous waste products in plasma are**
- T a. creatinine.
- T b. urea.
- F c. albumin.
- F d. amino acid.
- F e. cholesterol.

Q.06. **Viscocity of blood is**
- T a. related to haematocrit value
- T b. decreased in people with iron deficiency
- F c. related to temperature.
- F d. not increased in acclimatized mountaineer.
- F e. dependent on plasma protein only.

Q.07. **Hemopoietic stem cells are found in**
- T a. peripheral blood.
- T b. bone marrow.
- F c. kidney.
- F d. liver.
- F e. serum.

Q.08. **Growth and production of all stem cells are stimulated by**
- T a. interleukin-3.
- F b. interleukin-1.
- F c. growth hormone.
- F d. erythropoietin.
- F e. hypoxia.

Q.09. **Increased blood viscosity and slow circulation causes**
- T a. RBC rouleux formation
- F b. Increased plasma skimming
- F c. Increased number of RBC in capillaries
- F d. None
- F e. All of the above.

Q. 10. **D_2O (Deuterium oxide) is used to measure volume of**
- T a. Total body water
- F b. Blood
- F c. Extracellular fluid
- F d. Intracellular fluid
- F e. Plasma.

Q. 11. **Normal blood pH is**
- T a. 7.40
- F b. 7.20
- F c. 7.30
- F d. 7.70
- F e. 7.10

Q. 12. **Decreased MCHC is found in**
- T a. Microcytic hypochromic anemia
- F b. Megaloblastic anaemia
- F c. Sideroblastic anemia

F d. Vit B_{12} deficiency
F e. All of the above.

Serum/Plasma

Q.13. **Serum is**
T a. used for biochemical estimation
T b. a body fluid.
T c. associated with clot retraction
F d. plasma minus plasma protein
F e. is enriched with fibrin.

Q.14. **Plasma is**
T a. a clear yellowish fluid
T b. a colloid solution.
T c. freely inter changable with the intersitial fluid.
F d. one litre/square meter of body surface area.
F e. 45% of the volume.

Q.15. **Serum globulin**
T a. is synthesized in the liver.
T b. is increased in inflammatory condition.
T c. contributes to viscosity.
T d. acts as carrier protein.
F e. acts as hormone.

Q.16. **Plasma albumin**
T a. is negatively charged at normal pH of blood.
T b. contributes 80% of plasma colloidal osmotic pressure.
F c. is filtered freely at the renal glomerulus.
F d. carries oxygen in blood.
F e. lacks in essential amino acids.

Q.17. **Plasma bilirubin is**
T a. sensitive to light
T b. not ideal to cross *blood brain banier*
F c. a steroid pigment
F d. converted to biliverdin in liver
F e. freely filtered in the renal glomerulus.

Q. 18. **Colloidal osmotic pressure of plasma is due to**
T a. Albumin
T b. Globulin
F c. Fibrinogen
F d. Na^+ ion
F e. Potassium ion.

Q. 19. **Osmotic pressure is mainly due to**
T a. Albumin
F b. Glucose
F c. Clorides
F d. All
F e. None

Q. 20. **Oncotic pressure of plasma is due to**
T a. Albumin
F b. Prealbumin
F c. Electrolytes
F d. Fibrinogen
F e. Prothombin.

Q. 21. **Osmolatily of plasma in a normal adult (in m Osm/L) is :**
T a. 270 - 290
F b. 250 - 270
F c. 300 - 310
F d. 310 - 330
F e. 170 - 190

Q. 22. **The normal albumin/globulin (A/G) ratio in blood is**
T a. 2 : 1
F b. 5 : 1
F c. 1 : 2
F d. 1 : 1
F e. 3 : 1

Q. 23. **Which is true about serum albumin?**
T a. Contributes maximally to plasma oncotic pressure
T b. It is anionic
F c. Freely permeable in kidney
F d. Not synthesized in liver
F e. acts as hormone.

Q. 24. **Hemotocrit of venous blood is :**
T a. 3% greater than arterial blood
F b. 3 times greater than arterial blood
F c. 3% less than arterial blood
F d. 3 times less than arterial blood
F d. 4 times less than arterial blood

Red Blood Cell

Q.25. **Functions of RBC include**
T a. maintainance of viscosity of blood.
T b. acid base balance.
T c. supply of oxygen to tissues.
F d. maintainance of blood volume.
F e. carriage of nutrients.

Q.26. **The biconcave shape of RBC**
T a. helps it to squeeze through capillary.
T b. provides greater surface area than volume.
T c. can resist limited hypotonicity.
F d. allows it to float freely.
F e. provides increased fragility.

Q.27. **The total count of RBC depends upon**
T a. age and sex
T b. physcial activity

T c. hormonal factor
F d. nervous factor
F e. cytokines.

Q.28. **Total count of RBC is increased in**
T a. hypoxia.
T b. high altitude.
T c. increased testosterone level.
F d. anaemia.
F e. erythroblastosis foetalis.

Q.29. **Red blood cells in the peripheral blood**
T a. include about 1% reticulocytes.
F b. include about 1% nucleated cells.
F c. are distributed randomly in the stream of blood.
F d. travel at a slower speed in venules than capillaries
F e. are lower in hypoxic state.

Q.30. **Packed cell volume is**
T a. increased in bone marrow hyperplasia.
T b. measured by centrifugation of blood.
T c. determined by wintrobe method.
T d. increased after fluid loss.
F e. decreased in polycythemia.

Q.31. **Sites of RBC production in adult include**
T a. bone marrow.
F b. lymph node.
F c. kidney.
F d. lungs.
F e. blood vessels.

Q.32. **In adult, RBC is produced by the red bone marrow of**
T a. skull bone
T b. ribs
T c. sternum
F d. all long bones
F e. liver.

Q.33. **Erythropoetic factors are**
T a. hypoxia
T b. vitamin B_{12}
T c. vitamin C
T d. ACTH
F e. protein.

Q.34. **Maturation factor for erythropoiesis include**
T a. copper
F b. dietary protein
F c. cholesterol
F d. erythropoietin
F e. androgen.

Q.35. **Maturation of Red Blood cells are**
T a. due to diminished DNA.
T b. affected greatly by a persons nutritional status.
T c. mainly by Vitamin B12 and folic acid.
T d. failed due to lack of intrinsic factor.
F e. not failed due to lack of intrinsic factor.

Q.36. **Maturation of RBC means**
T a. synthesis of Hb
T b. cytoplasm transforming from basic to acidic stain
F c. cells are old
F d. cells are larger in size
F e. presence of mitochondria in the cytoplasm.

Q.37. **Erythropoiesis is regulated by**
T a. rate of erythrocyte destruction
T b. erythropoietin
T c. vitamin-B_{12}
T d. androgen
F e. blood pressure.

Q.38. **Erythropoietin**
T a. stimulates RBC production.
T b. is secreted in response to hypoxia.
T c. is secreted from kidney.
F d. is activated in lung.
F e. is a chromoprotein.

Q. 39. **Biconcave shape of RBC's, is helpful because**
T a. Increased surface area for a given diameter
F b. Easily passage through capillaries
F c. Rouleax formation
F d. None
F e. None.

Q. 40. **Mean life (days) of RBCs in transfused blood is**
T a. 60
F b. 120
F c. 100
F d. 90
F e. 60.

Q. 41. **Life span of RBC is**
T a. 120 days
F b. 90 days
F c. 60 days
F d. 30 days
F e. 60 days

Hemoglobin

Q.42. **Hemoglobin is**
T a. a chromoprotein.
F b. a glycoprotein.
F c. present in myofibril.
F d. synthesized in endoplasmic reticulum.
F e. lipid soluble.

Q.43. **Hb synthesis requires**
- T a. iron
- T b. vit-C
- T c. glycine
- T d. protoporphyrin IX
- F e. vit-D.

Q.44. **Hemoglobin chain are normal in structurein**
- T a. thalassemia
- F b. sickle cell anaemia
- F c. pernicious anaemia
- F d. haemolytic anaemia
- F e. chronic blood loss.

Q. 45. **Most of the Hb synthesized during the developmental stage is**
- T a. normoblast
- F b. pronormoblast
- F c. reticulocyte
- F d. proerythroblast
- F e. erythrocyte.

Q.46. **Abnormal hemoglobins are**
- T a. HbC
- F b. Hb A
- F c. Hb F
- F d. methemoglobin
- F e. reduced hemoglobin.

Q.47. **Foetal hemoglobin**
- T a. binds easily with 2,3-DPG
- T b. is alkali resistant
- T c. has higher P50
- T d. can be found after birth
- F e. has low affinity for oxygen.

Q.48. **Foetal hemoglobin**
- T a. can bind 2,3-DPG more avidly.
- F b. is present in blood up to adolescent age.
- F c. has high affinity for CO_2.
- F d. can release oxygen very easily.
- F e. consists of 2α and 2β chain.

Q.49. **When fully saturated, 1gm pure Hb can combine with**
- T a. 1.39 ml of oxygen.
- F b. 1.33 ml of oxygen.
- F c. 1.34 ml of oxygen.
- F d. 1.32 ml of oxygen.
- F e. 1.35 ml of oxygen.

Q.50. **Oxygenation of hemoglobin means**
- T a. reversible binding of oxygen with hemoglobin.
- T b. loose combination with Hb.
- T c. formation of noncovalent bond.
- T d. combination with molecular oxygen.
- F e. loss of electron from haem.

Q. 51. **Carbon monoxide combines with**
- T a. Heam part of hemoglobin
- F d. Plasma
- F c. Epididymis
- F b. Globin part of hemoglobin
- F e. Albumin.

Q. 52. **Haemoglobin unlike myoglobin shows**
- T a. Parabolic curve of oxygen association
- F b. Positive cooperativity
- F c. Cooperative index of 81
- F d. Hill's coefficient of 1
- F e. None.

Q. 53. **Myoglobin binds with**
- T a. 1 mol of oxygen per mol
- F b. 2 mol of oxygen per mol
- F c. 3 mol of oxygen per mol
- F d. 4 mol of oxygen per mol
- F e. 2.5 mol of oxygen per mol

Q. 54. **The best method for estimation of Hb concentration in blood is**
- T a. Cyanmethaemoglobin method
- F b. Acid haemalion method
- F c. Alkali haematin method
- F d. All of the above
- F d. None of the above

ESR

Q.55. **ESR**
- T a. is increased in tuberculosis.
- T b. can be measured by Westergren method.
- F c. is normal in pregnancy.
- F d. has more diagnostic value than prognostic value.
- F e. is decreased in malignancy.

Q. 56. **Buffy coat contains**
- T a. leukocytes and platelets.
- F b. myelin.
- F c. actin myosin.
- F d. sarcolemma.
- F e. glycocalyx.

Q.57. **ESR is increased**
- T a. during muscular exercise.
- T b. during pregnancy.
- T c. during manstruation.
- F d. in afibrinogenemia.
- F e. in blood coagulation.

Iron & Fate of RBC

Q. 58. **Old RBC is removed from circulation by**

T a. liver and spleen
F b. liver only
F c. spleen only
F d. bone marrow only
F e. spleen, liver and bone marrow

Q.59. **Hemolysis of normal RBC is caused by**
T a. hypotonic solution.
T b. toxin.
T c. malaria.
T d. antigen antibody reaction.
F e. spherocytosis.

Q.60. **Iron containing compounds in our body are**
T a. catalase.
T b. cytochrome oxidase.
T c. myoglobin.
F d. immunoglobin.
F e. thyroglobulin.

Q.61. **Transferrin**
T a. is a plasma protein.
T b. carries iron in the blood.
T c. is synthesized in the liver.
F d. is an iron contianing enzyme.
F e. is an intracellualr protein.

Q.62. **Ferritin content is increased in**
T a. excess iron intake.
F b. iron deficiency.
F c. high protein diet.
F d. hemorrhagic condition.
F e. prolonged illness.

Q.63. **Rate of iron absorption depends on**
T a. storage of iron in the body.
T b. chemical convrsion of dietary iron.
T c. loss of body iron.
F d. availability of transferrin only.
F e. state of circulation.

Q. 64. **Iron is stored in the body in the following**
T a. RE system
T b. Spleen
T c. Bone marrow
F d. Gall bladder
F e. None.

Q. 65. **Iron is store in**
T a. Reticuloendothelial system
F b. RBC
F c. Plasma
F d. Gall bladder
F e. All.

Anaemia

Q.66. **Iron deficiency anaemia**
T a. is characterized by reduced Hb concentration.
T b. is produced by malnutrition.
T c. occurs due to vitamin C defiency.
F d. is more common in male than female.
F e. may be associated with increased size of RBC.

Q.67. **Pernicious anaemia**
T a. is caused by poor vitamin B_{12} absorption.
T b. may follow partial gastrectomy.
T c. is characterized by megaloblastic erythropoiesis.
F d. occurs in prolonged illness.
F e. is caused by chronic hemorrhage.

Q.68. **Functions of intrinsic factor are**
T a. carriage of vitamin B_{12} in the gut.
T b. protection of vitamin B_{12} from digestion.
F c. increasing the solubility of vitamin B_{12}.
F d. promotion of excretion of vitamin B_{12}.
F e. neutralization of acid.

Q.69. **Sickle cell anaemia is produced**
T a. due to abnormal erythropoiesis.
T b. in hypoxic condition.
T c. due to genetic defect.
T d. by excessive hemolysis.
F e. due to formation of normal amino acid chain.

Q.70. **Hemoytic anaemia occurs in**
T a. erythroblastosis foetalis.
T b. vitamin B_{12} deficiency.
T c. hereditary spherocytosis.
T d. hemoglobinopathy.
F e. thalassemia.

Q.71. **Sickle cell anemia**
T a. has abundant HbS
T b. has abundant crystals of Hb in RBCs.
T c. contains abnormal hemoglobin
F d. is less prevalent in African-Americans
F e. is not a kind of hemo]ytic anemia

Q.72. **Hemorrhagic anaemia may be characterized by**
T a. microcytic hypochromic anaemia.
T b. macrocytic anaemia.
T c. normocytic hypochromic anaemia.
T d. normocytic normochromic.
F e. reticulocytosis.

Q.73. **Laboratory classification of anaemia is done on the basis of**
T a. MCV.
T b. TC of RBC.
T c. Hb%.

T d. PCV.
F e. ESR.

Q.74. **Polycythemia**
T a. produces increased blood volume.
T b. is associated with reddish colour with bluish tint.
T c. causes increased viscosity of blood.
F d. causes increased blood flow.
F e. causes increased cardiac output.

Q. 75. **In anemia, the concentration of 2, 3-DPG is:**
T a. Increased
F b. Decreased
F c. A or b
F d. Not changed
F e. None.

Q. 76. **Patient with anaemia tends to have**
T a. Compensatory increase in cardiac output
T b. Increased incidence of heart murmurs
T c. Pallor of mucous membranes
F d. A low PO_2 in arterial blood
F e. None.

Jaundice

Q. 77. **In haemolytic jaundice**
T a. urinary bilirubin is absent.
T b. Vadenbergh test is indirect.
T c. faecal stercobilinogen is increased.
F d. urinary urobilinogen is decreased.
F e. liver function is impaired.

Q. 78. **In hepatic jaundice**
T a. Vandenbergh test is biphasic.
T b. faecal stercobilinogen is decreased.
F c. urinary urobilinogen is increased.
F d. bilirubin in urine is absent.
F e. liver function is normal.

Q. 79. **In obstructive jaundice**
T a. urinary bilirubin is present.
T b. Vendenbergh test is direct.
F c. faecal stercobilinogen is present.
F d. urinary urobilinogen is present.
F e. liver function is impaired.

Q. 80. **A premature infant is more likely than a full term infant to**
T a. Excrete urine with a uniform specific gravity
T b. Suffer from anaemia.
T c. Suffer from jaundice of hepatic origin
F d. Maintain a normal body temperature in a cold environment
F e. None.

White Blood Cell

Q. 81. **Blood cells that are not formed in bone marrow include**
T a. plasma cell.
F b. erythrocytes.
F c. monocytes.
F d. thromobocytes.
F e. granulocytes.

Q. 82. **Stem cells giving rise to granular leukocytes are**
T a. myeloblast.
F b. erythroblast.
F c. lymphoblast.
F d. megakaryoblast.
F e. normoblast.

Q.83. **Granules of granulocyte contains**
T a. anticoagulant.
F b. enzymes.
F c. toxins.
F d. vasoactive substances.
F e. local hormones.

Q.84. **Neutrophils**
T a. move freely to site of inflammation
T b. are phagocytic cells
T c. are chemotactic cells
F d. are less motile
F e. are fewer in lysosome.

Q.85. **Neutrophil count rises**
T a. during infection.
T b. during exercise.
F c. in allergic raction.
F d. in dehydration.
F e. during haemorrhage.

Q.86. **Basophil**
T a. secretes substances that increase capillary penneability
T b. releases histamine when they degenerate.
T c. is stimulated by antigen bound to IgE
F d. is the most abundant granulocyte in peripheral blood
F e. is suppressed by complement opsonin

Q.87. **Parasiticidal WBC is**
T a. esinophil.
F b. macrophage.
F c. neutrophil.
F d. monocyte.
F e. lymphocyte.

Q.88. **Monoeytes**
T a. are highly motile

T b. are phagocytie cells
F c. are uniformly spherical
F d. manufacture 1gM
F e. originate from precursor cells in lymph nodes.

Q.89. **Lymphocytes**
T a. are concerned with cell mediated immunity.
T b. produce interleukin.
T c. are produced in lymphoid tissue.
T d. are produced in bone marrow.
F e. induce passive immunity.

Q.90. **B lymphocytes are**
T a. converted into plasmoblast.
T b. activated by macrophage.
F c. processed after birth.
F d. are named after bone marrow.
F e. concerned with innate immunity.

Q.91. **Helper T cells**
T a. secrete interleukin
T b. stimulate growth of other T cells
T c. activate macrophages
T d. stimulate growth and differentiation of B cells
F e. are out numbered by cytotoxic T cells.

Q.92. **Suppressor T cells**
T a. never become plasma cells.
T b. play a role in tolerance.
F c. secrete lymphokines.
F d. prevent activation of complement cascade.
F e. more than 75% of the T cells are suppressor.

Q. 93. **B lymphocytes are associated with**
T a. CD 35
F b. CD 19
F c. CD 27
F d. CD 4
F d. CD 8

Q. 94. **Secondary granules of neutrophils contain**
T a. Lactoferin
F b. Catalase
F c. Myeloperoxidase
F d. Nucleotidase
F e. None.

Q. 95. **The function common to neutrophils, monocyte and macrophage is**
T a. Phagocytosis
F b. Immune response
F c. Liberation of histamine
F d. Destruction of old erythrocytes.
F e. None.

Q. 96. **Eutropenia is seen in all except :**
T a. Trauma
F b. Pernicious anaemia
F c. Severe bacterial infection
F d. Bone marrow depression
F e. None.

Q. 97. **Macrophages are the mature form of**
T a. Monocytes
F b. Neutrophils
F c. Eosinophils
F d. Basophils
F e. Lymphocytes

Q. 98. **Which one of the following statements about lymphocytes is incorrect?**
T a. Concentration falls in the blood abruptly and immune reaction is disturbed after removal of thymus in adult
F b. Produced by thymus, red bone marrow, spleen and lymph nodes
F c. Probably change into plasma cells
F d. Constitute 20-40% of leukocytes
F e. Do not perform an important phagocytic function

Q. 99. **Which one of the following statements concerning the monocyte is incorrect?**
T a. Unlike neutrophil does not accumulate outside circulation in area of inflammation
F b. More common in blood than eosinophil and basophil
F c. Produced in the adult by the bone marrow and lymph nodes
F d. Not classified as a granulocyte
F e. None.

Q. 100. **Arneth count is**
T a. Counting the lobes in the neutrophil
F b. Counting the lymphocytes
F c. Counting the granules in the eosinophil.
F d. WBC counting in bone marrow.
F e. None.

Immunity

Q.101. **Immunity**
T a. cause damage to body tissue in some disease.
T b. is responsible for transplantation reaction
F c. produces generalised weakness.
F d. helps in invasion by bacteria.
F e. helps in hemostasis.

Q. 102. **Mode of actions of complement are**
T a. opsonization.
T b. agglutination.

T c. lysis.
T d. phagocytosis.
F e. enzyme activation.

Q.103. **Cell mediated immunity is mediated by**
T a. T lymphocyte.
F b. macrophage.
F c. neutrophil.
F d. B lymphocyte.
F e. plasma cell.

Q. 104. **Complement protein**
T a. activates mast cells and basophlis.
T b. activates phagocytosis
T c. activates chemotaxis
T d. causes cellular lysis (cytolytic)
F e. is weakly activated by antigen-antibody complex

Q.105. **Principle of vaccination is**
T a. activation of clone of lymphocyte.
T b. memory cell production.
F c. antigen antibody complex formation.
F d. antibody production only.
F e. proliferation of lymphocytes.

Q.106. **Immunoglobulin that crosse placenta are**
T a. IgG
F b. IgA
F c. IgD
F d. IgM
F e. IgE.

Q.107. **Antibody attacks foreign invader by**
T a. preciptation.
T b. lysis.
F c. chemotaxis.
F d. clotting
F e. toxin.

Q.108. **Most powerful mode of action of antibody is**
T a. activated complement system.
F b. supressor T cells.
F c. cytotoxic T cells.
F d. helper T cell.
F e. macrophage.

Q.109. **Chief regulatory cell of immunity are**
T a. helper T cell.
F b. suppressing T cells.
F c. cytotoxic T cells.
F d. activated B cell.
F e. macrophage.

Q.110. **Immune tolerance is responsible for**
T a. absence of antibody against antigen.
F b. autoimmune disease.
F c. all inflammatory condition.
F d. rejection of organ transplantation.
F e. allergic condition.

Q. 111. **Antigen presenting cells are specialised cells present on the followings**
T a. Skin
T b. Lymph node
T c. Spleen
F d. Kidney
F e. Liver.

Q. 112. **MHC class II antigens are located on which of the following cells?**
T a. Dentritic cells of the spleen
T b. Macrophages
T c. Langerhans cells of skin.
T d. B cells
F e. Platelets

Q. 113. **Immune complexes are removed from blood by**
T a. Kupffer cell
F b. B cell
F c. Basophil
F d. Plasma cell
F e. T cell.

Q. 114. **phagocyttosis in the CNS is done by**
T a. Microglia
F b. Astrocytes
F c. Schwann cells
F d. Oligocytes
F e. Macrophage.

Q. 115. **Immunity is most suppressed in**
T a. Patients on ACTH therapy
T b. In AIDs
F c. Liver failure
F d. Anemia
F e. Renal failure

Q. 116. **T-Lymphocyte**
T a. Mature in lymphnodes
F b. Produce antibodies
F c. Comprise 10 to 15% lymphocytes
F d. Principal cells in lymphnode cortical centre.
F e. None.

Inflammation

Q.117. **Tissue inflammation produces**
T a. change in vascular diameter.
T b. change in vascular permeability.
T c. migration of WBC.
T d. chemotactic agents.
T e. oedema.

Q.118. **Inflammatory agents are**
- T a. histamine.
- T b. serotonin.
- F c. adrenaline.
- F d. fibrinogen.
- F e. albumin.

Q.119. **Host response to inflammation includes**
- T a. coagulation of extracellular fluid.
- T b. acute neutrophilia.
- F c. acute polycythemia.
- F d. inactivation of macrophage.
- F e. endothelial proliferation.

Q.120. **The phagocytic cells are**
- T a. macrophage.
- T b. neutrophil.
- T c. eosinophil.
- F d. endothelial cell.
- F e. epithelial cell.

Q. 121. **Nitric oxide is produced in**
- T a. Endothelium
- F b. Plasma
- F c. Platelets
- F d. Serum
- F e. Blood.

Q. 122. **Thromboxane A_2 is mainly produced by**
- T a. Platelets
- F b. Vascular endothelium
- F c. Liver
- F d. Damaged tissue.
- F e. None.

Q. 123. **SRS-A is a**
- T a. Leukotriene
- F b. Seratonin
- F c. Histamine
- F d. Prostaglandin
- F e. None.

Q.124. **Leukemia**
- T a. produces increased hemorrhagic tendency.
- T b. causes decreased body defense.
- T c. causes anaemia.
- F d. causes increased coagulation time.
- F e. may cause depletion of normal tissue protein.

Q. 125. **Pyrogens raise body temperature by**
- T a. Releasing interleukins
- F b. Setting the the thermostat to higher level
- F c. Decreasing peripheral heat liberating mechanism
- F d. Causing peripheral vasoconstriction
- F e. None.

Platelet

Q.126. **Platelets**
- T a. form plug by sticking to each other.
- T b. release vasoconstrictor agents.
- T c. store Ca+ in granules.
- T d. provide phospholipid for intrinsic pathway.
- F e. are destroyed by osmotic force.

Q.127. **Platelets**
- T a. have role in blood coagulation.
- T b. liberate 5-HT.
- T c. help in phagocytosis.
- T d. secrete ADP.
- F e. liberate immunoglobulins.

Q.128. **Proteins produced by platelets include**
- T a. thromboplastin.
- F b. plasminogen.
- F c. fibrinogen.
- F d. prothrombin.
- F e. casinogen.

Q. 129. **Aggregins are**
- T a. Meant for platelet aggregation
- F b. For adhesion of cells to basement membrane
- F c. For adhesion of fibrinogen receptors to platelets
- F d. For platelet adhesion to endothelium.
- F e. None.

Q. 130. **A reliable screening test for platelet function is**
- T a. Clot retraction time
- F b. CT
- F c. PT
- F d. Thrombin time
- F e. None.

Q. 131. **Thromboxane A2 is released mainly by the**
- T a. Platelets
- F b. Vascular endothelium
- F c. Liver
- F d. Muscles
- F e. Kidney.

Q. 132. **Half life of transfused platelets is**
- T a. 8 days
- F b. 4 Hours
- F c. 12 Hours
- F d. 15 days
- F d. 10 days.

Blood group

Q.133. **ABO blood group antigens are**
- T a. present since birth.

T b. agglutinogen in prsence of corresponding antibody.
F c. found in the plasma.
F d. protein in nature.
F e. determined for tissue typing.

Q. 134. **Blood group antigens are**
T a. present in fetal blood
T b. present in red cells membrane.
F c. carried on the Hb molecules
F d. immunoglobins
F e. regularly immunogenic

Q.135. **All agglutinins are**
T a. present in O blood group.
T b. formed after birth.
F c. present in all blood groups.
F d. present in AB blood group.
F e. present since birth.

Q. 136. **Antibodies against both group A and group B antigens are found in the blood plasma of a person who possesses**
T a. group O.
F b. group A.
F c. group B.
F d. group AB.
F e. Rh positive blood.

Q.137. **A person with group A (+ve) blood**
T a. has A agglutinogen in the red blood cell membrane.
T b. has anti-A antibody in the plasma.
T c. has 'D' agglutinogen in the RBC membrane.
F d. may have the genotype AB.
F e. can donate blood to a person with group B +ve blood.

Q.138. **Rh+ve blood group is safer than Rh-ve because it**
T a. can receive both Rh-positive and Rh negative blood
T b. has no antibody.
T c. does not produce antibody against Rh negative.
T d. can not receive Rh-negative blood.
F e. can be given to Rh-negative person.

Q.139. **Erythroblastosis fetalis**
T a. is due to destruction of RB Cs.
T b. leads to neonatal jaundice.
T c. leads to hepatomegaly.
T d. leads to splenomegaly.
F e. is common in Rh+ve mother.

Q. 140. **Stored blood as compared to fresh blood has**
T a. High extracellular K^+
F b. More 2,3 DPG
F c. High extracellular Hb
F d. Increased platelets.
F e. Less 2,3 DPG

Q. 141. **True about Rh factor**
T a. Has no naturally occuring antibody
F b. Seen only in humans
F c. Not important for blood transfusion
F d. None
F e. All.

Q. 142. **Addition of glucose to stored blood is to**
T a. Increase 2,3 DPG
F b. Prevent hemolysis
F c. Provide nutrition
F d. In crease Hb content
F e. All.

Q. 143. **Blood group antigens are**
T a. Found in saliva
F b. Carried by sex chromosomes
F c. Attached to plasma proteins
F d. Attached to Hemoglobin molecule
F e. All.

Q. 144. **AB blood group antigen are known as factors**
T a. Landsteiner
F b. Duff
F c. Rhesus
F d. Lutheran
F e. Kidd.

Coagulation of blood

Q.145. **Granules of granulocyte contains**
T a. anticoagulant.
F b. enzymes.
F c. toxins.
F d. vasoactive substances.
F e. local hormones.

Q. 146. **The activation of factor X is**
T a. essential for prothombin activation.
T b. part of both extrinsic and intrinsic pathway.
F c. part of the intrinsic pathway only.
F d. part of the extrinsic pathway only.
F e. essential for activation of Christmas factor.

Q.147. **Thrombin**
T a. combines with antithrombin III.
T b. is removed by antithrombin III.
T c. is accelerated by factor V.
F d. removes clot from circulation.
F e. converts plasminogen to plasmin.

Q.148. **Chemical factors related to hemostasis are**
T a. serotonin.
T b. thrombaxane A_2.

F c. adrenalin.
F d. prostaglandin.
F e. leukotrein.

Q.149. **Coagulation of blood requires**
T a. platelet.
T b. calcium ion.
T c. Vitamin K.
F d. Vitamin C.
F e. inactivation of heparin.

Q.150. **Essential clotting factors are**
T a. Calcium ion.
T b. Fibrinogen.
T c. Prothrombin.
T d. Thrombin.
F e. Hageman factors.

Q.151. **Vitamin K is necessary for synthesis of**
T a. Factor IX.
T b. Factor X.
T c. Prothrombin.
F d. Factor V.
F e. fibrinogen.

Q.152. **Platelet plug**
T a. is composed of swollen and aggregated platelets.
T b. forms platform for deposition of fibrin thread.
T c. stops bleeding from injured tiny vessels.
T d. formation is facilitated by ADP.
F e. is induced by Ca^{++}

Q. 153. **Prothrombin activator is formed by**
T a. activated factor X
T b. tissue phospholipids
T c. factor V
F d. activated factor XII
F e. vitamin K.

Q.154. **Extrinsic mechansim of clot formation is**
T a. initiated by release of tissue factor from injured cell membrane.
T b. a vicious process.
F c. responsible for blood clot in test tube.
F d. involved with activated factors VIII.
F e. a slow process.

Q.155. **Intrinsic pathway of coagulation begins with tmuma to the**
T a. blood itself
F b. vassel wall
F c. damaged tissues
F c. collagen fibers
F d. skin.

Q.156. **Convesrsion of fibrinogen to fibrin is**
T a. followed by polymerization of fibrin monomers.
T b. effected by thrombin.
F c. effectd by prothrombin.
F d. activated by Heparin.
F e. reversed by plasma.

Q.157. **Clotting time is**
T a. the time required for activation of clotting factors.
T b. a test for bleeding disorder.
F c. increased in thrombocytopenia.
F d. decreased in hemophilia.
F e. 15 minutes in a normal person.

Q.158. **Bleeding time is**
T a. prolonged in low platelet count.
T b. an indicator of natural hemostatic mechansim.
T c. normal in hemophilia.
T d. 1-6 minutes in normal person.
F e. the time required for coagulation of blood in a wound after injury.

Q.159. **Fate of a clot is**
T a. calcification.
T b. fibrous organization.
T c. lysis.
T d. resolution.
F e. not enzymatic destruction.

Q.160. **Clot retraction**
T a. is responsible for recanaliation of vessel.
T b. leads to serum formation.
T c. is contributed by platelet.
T d. gives an idea about platelet count.
F e. is related to Ca^{++} concentration.

Q. 161. **In the blood in a test tube, after clot retraction there is formation of**
T a. serum.
F b. tissue fluid.
F c. lymph.
F d. plasma.
F e. transcellualr fluid.

Q.162. **Serum is**
T a. used for biochemical estimation.
T b. associated with clot retraction.
T c. a body fluid.
F d. is enriched with fibrin.
F e. plasma minus plasma protein.

Q.163. **Factors maintaining fluidity of blood in the circulation are**
T a. thrombomodulin complex.
F b. rough endothelium.
F c. reynold's number.

F d. antibody.
F e. plasmin.

Q.164. **Plasmin is**
T a. causing fibrinolysis.
F b. involved in intrinsic clotting system.
F c. involved in extrinsic clotting system.
F d. promoting formation of emboli.
F e. found in serum.

Q.165. **Plasminogen is**
T a. activated by tissue plasminogen activator (TPA)
T b. associated with clot lysis.
F c. produced in plasma cell.
F d. a vasodilator.
F e. concerned with platelet activation.

Q.166. **Profibrinolysin**
T a. is synthesized by hepatic cell.
T b. remains inhibited in circulation.
F c. converts fibrinogen into fibrin.
F d. is an active proteolytic enzyme.
F e. helps in platelet plug formation.

Q.167. **Followings are anticoagulants**
T a. double oxalate.
T b. heparin.
T c. 3.8% sodium citrate.
F d. n/10 HCI.
F e. normal saline.

Q.168. **Heparin is**
T a. produced by mast cell.
F b. a procoagulant.
F c. an enzyme.
F d. protein in nature.
F e. synthesized by palsma cell.

Q.169. **Heparin prevents blood coagulation primarily because it**
T a. blocks the action of thrombin.
F b. dissolves fibrinogen.
F c. blocks conversion of prothrombin to thrombin.
F d. activates thromboplasin.
F e. chelates calcium.

Q.170. **Heparin prevents clotting primarily because it**
T a. blocks the action of thrombin.
F b. dissolves fibrinogen.
F c. blocks conversion of prothombin to thrombin.
F d. activates thromboplstin.
F e. chelate Ca^{++}.

Q.171. **Warfarrin is**
T a. an anticoagulatn.
T b. vitamin K antagonist.
F c. an antibiotic.
F d. used in hemorrhagic condition.
F e. protein in nature and binds with calcium.

Q.172. **Tests for bleeding disorder are**
T a. coagulation time.
T b. bleeding time.
T c. thromboplastin generation time.
T d. platelet count.
F e. RBC count.

Q.173. **Causes of bleeding are**
T a. vitamin -K deficiency
T b. hemophilia
T c. thrombocytopenia
F d. anaemia
F e. cyanosis.

Q.174. **In purpura there are**
T a. bleeding under skin.
T b. prolonged bleeding time.
T c. indication of weak hemostatic mechanism.
F d. skin pigmentation.
F e. leucopenia.

Q. 175. **In Christmas disease**
T a. blood fails to coagulate properly
F b. hematocrit is low
F c. few red cells are produced
F d. ESR is raised
F e. factor VIII is deficient

Q.176. **Hemophilia is**
T a. a genetic disorder.
T b. lack of factor VIII.
F c. a dvelopmental abnormality.
F d. caused by defective autosome.
F e. more common in female.

Q. 177. ***Haemophilia A is associated with all except**
T a. Increase PT
F b. Soft tissue haematoma
F c. Pseudotumor
F d. Increase PTT
F e. None.

Q. 178. **In Hemophilia**
T a. Factor VIII is decreased
T b. Cloting time is increased
F c. Factor VII is decreased
F d. Bleeding time is increased
F e. Prothrombin time is increased

Q. 179. **Hemophilia is due to deficiency of factor**
T a. VIII
F b. II

F c. V
F d. XIII
F e. IX.

Q. 180. **The best screening test for hemophilia is :**
T a. PTT
F b. BT
F c. PT
F d. CT
F e. CRT

Q. 181. **To prolong Lee White clotting time in a patient for the next eleven hours what would be the procedure of choice**
T a. IV heparin
F b. IV sodium citrate
F c. IV vitamin K
F d. Dicumarol therapy
F e. CRT

Q. 182. **The normal non-fasting blood ketone level is**
T a. 2-10 mg%
F b. 0.1-0.5 mg%
F c. 0.5-2 mg%
F d. 100-500 mg%
F e. 0.2-1.00 mg%

Q. 183. **A procoagulant not normally circulating in the plasma is**
F a. Prothrombin
F b. Fibrinogen
F c. Antihemophilic factor
F d. Factor V
T e. None of the above

Q. 184. **Which one of the following is released by blood platelets during haemorrhage to produce vasoconstriction?**
T a. Serotonin
F b. Histamine
F c. Thrombosthenin
F d. Accelerator globulin
F e. Bradykinin

Q. 185. **Endothelial cells synthesize**
T a. Factor VII
F b. Fibrinogen
F c. Factor X
F d. Factor XII
F e. Factor IX

Q. 186. **In vitro coagulation is initiated by factor**
T a. XII
F b. XI
F c. X
F d. VII
F e. IX

Q. 187. **Anaphylaxis is mediated by all except**
T a. Serotonin
F b. Bradykinin
F c. Anaphylotoxin
F d. Prostaglandin.
F e. Leukotrin.

6
Cardio Vascular System

Heart

Heart is a central pumping organ. It receives and pumps out blood to the whole body.

1. *Shape :* Conical or roughly heart shaped (like heart of playing cards)
2. *Size :* 12 cm from base to apex.
   6 cm antero-posteriorly.

Situation : Situated in the middle mediastinum in between the two lungs, obliquely placed behind the body of sternum and the adjoining portions of ribs and cartilages: about one third of it is on the right side and two third of it on the left side of the middle.

Parts of the heart

Heart has got four chambers, with some openings. The chambers are-

a. Right atrium
b. Left atrium — *Receiving chambers*

c. Right ventricle
d. Left ventricle. — *Distributing chambers*

Openings of the heart

Heart has got four openings :

a. *Right atrioventricular opening :* Lies between right atrium & right ventricle and is guarded by right atrioventricular (tricuspid) valve.

b. *Left atrioventricular opening :* Lies between left atrium and left ventricle and is guarded by left atrioventricular or mitral (bicuspid) valve.

c. *Pulmonary opening :* Lies between right ventricle & pulmonary trunk and guarded by semilunar valve.

d. *Aortic opening :* Lies between Left ventricle and ascending aorta and is guarded by semilunar valve.

Valves of the heart

There are four valves in heart -

a. *Right atrioventricular valves :* It is also called tricuspid as it has three cusps. The cusps are -
   i. Anterior or infundibular
   ii. Posterior or marginal
   iii. Medial or septal

b. *Left atrio-ventricular valve :* It is also called mitral (due to its resemblance to a bishop mitre) or bicuspid valve as it has two cusps. The cusps are -
   i. Anterior or aortic
   ii. Posterior

c. *Semilunar valves :* Two in number, one in aortic and another in pulmonary opening. They each have three cusps. They are so called as semilunate in shape.

Functions of valves :

1. Valves help in the flow of blood in one direction.
2. Prevent regurgitation of back flow of blood by their direction during opening and closure.
3. They are concerned with the production of heart sound.

Precardium : The area of the anterior chest wall that overlies the heart is called precardium.

Nerve Supply

Q. 00. **What is the nerve supply of heart.**

Ans. *Nerve supply to the heart are* :

i. *Parasympathetic nerve* :
   a. *Nerve fibers* : Arise from nucleus abbiguus (medulla) → join vagus and finally terminate on heart;
   b. *Neurotransmitter* : Acetylcholine.
   c. *Effect* : Cardiac inhibition.

ii. *Sympathetic nerve* :
   a. *Nerve fibers* : Arise from LHC of upper thoracic but specially from T_3 & T_4; LHCs are controlled by VMC (medulla)
   b. *Neurotransmitter* : Noradrenalin
   c. *Effect* : Cardiac stimulation.

Cardiac or rather cardiovascular reflexes : operate via sympathetic and to some limited extent by parasympathetic nerves. Well known reflexes include -

i. *broreceptor*
ii. *chemoreceptor*
iii. *atrial* and
iv. *Bezold Jarisch reflexes.*

All these reflexes change heart rate, many of them change the blood pressure and some even the respiration; all of them restore the homeostasis.

Q. 06. ***List the effects of stimulation of sympathetic and parasympathetic systems on the heart.**

	Parasympathetic	*Sympathetic*
Heart (β_1, β_2) : a. *S-A node*	Decrease in heart rate, vagal arrest.	Increase in heart rate

	Parasympathetic	*Sympathetic*
b. *Atria*	Decrease in contractility and (usually) increase in conduction velocity.	Increase in contractility and conduction velocity
c. *A-V node*	Decrease in conduction velocity	Increase in conduction velocity.
d. *His-Purkinje system*	Decrease in conduction velocity	Increase in conduction velocity.
e. *Ventricles*	Decrease in contractility.	Increase in contractility
Arterioles : a. Coronary	Dilatation	Constriction (α_1, α_2) Dilation (β_2).

Q. ***Heart receives its blood supply during diastole- Explain.***

Ans. During diastole of heart, cardiac muscles are relaxed, intramural tension decreases and coronary blood vessels are less compressed. So, blood can easily enters into coronary vessels and supply blood. On the other hand, during systole, due to increase cardiac muscular tension, coronary vessels are compressed. So, heart gets its boold supply during diastole.

Heart Muscles

Physiology of cardiac muscle :The heart is composed of three major types of cardiac muscle -

a. Atrial muscle
b. Ventricular muscle
c. *Spcialized excitatory and conductive muscle fibres-*
   i. The sinus node (sino-atrial or SA node)
   ii. The internodal pathway
   iii. The A-V node (Atrio-ventricular node)
   iv. The A-V bundle
      1. Penetrating portion
      2. Distal portion
   v. The left and right bundles of purkinje fibers.

N.B. SA node, internodal pathways, AV node, Bundle of His & its branches, purkinje fibers *(Ref. Ganong 22th ed)*

The atrial and ventricular muscle contract, in which the duration of contraction is much longer.

The specialized excitatory and conductive muscle fibers contract very feebly as they contain few contractile fibrils: and exhibit rhythmicity and varying rates of conduction.

(Ref. Guyton 11th ed; page 103)

Functional anatomy of muscle

Myocardial cells (=fibers) are of 2 types-

i. *Pace maker and conducting cells* (=SAN,AV junctional tissue , bundle of His and its branches, purkinje's fibers) : They generate impulse and conduct the impules

ii. *Working myocardial cells* (WMC) : Which contract. WMC consists of myofibrils; each myofibril cosists of 4 types of myofilaments :
   i. Actin
   ii. Myosin
   iii Tropomyosin
   iv. Troponin.

At rest, the active sites of actin (where myosin heads are to be attached during contraction), are covered by tropomyosin.

2 types of tubules are seen in sarcolemma (=cell membrane of muscle fiber)- i. T tubules which communicate with the ECF, and ii. L tubules (=sarcoplasmic reticulum) which do not communicate with the exterior. T tubules occur near the Z lines (which form the boundaries of sarcomere) and near them L tubules form cisterns (or triads).

Syncytium

It means a group of cells in which the protoplasm of one cell is continuous with that of adjoining cells such as the mesenchyme cells of embroys, striated muscle fibre.

Heart muscle cells are large and branching. They are connected to each other by angulated dark areas crossing the cardiac muscles fibre are called intercalated discs; however, they are actually cell membranes that separate individual cardiac muscle cells from each other. That is cardiac muscle fibres are made up of many individual cells connected in series with each other. The intercalated disc exerts a very little resistance (1/400th of normal), which resembles that there is no membrane in between the cardiac muscle cells, because the cell membranes fuse with each other and form very permeable junctions (*gap junction*) that allow relatively free diffusion of ions. Therefore, from a functional point of view, ions move with ease along the axes of the cardiac muscle fibres so that action potentials travel from one cardiac muscle cell to another, past the intercalated discs, with only slight hindrance. Therefore, cardiac muscle is a syncytium.

The heart is composed of two separate syncytiums; the atrial syncytium that constitute the walls of two atria & the ventricular syncytium that constitute the wall of two venticule.

(Ref. Guyton & Hall-11th Edition; page 103, 104)

Junctional tissues of heart

Cardiac muscle consist especially of certain specialized structures which are responsible for initiation and transmission of cardiac impulses at a regular and faster rate than rest of the muscle. These are called junctional tissue of heart.

Junctional tissues are :

i. The sinus node (Sino-atrial or SA node)

ii. The internodal atrial pathway.
iii. The AV node (Atrio-ventricular node)
iv. The bundle of His and its branches.
v. Purkinje system.

SA node or sino-atrial node

Situation : It is situated in the right atrium at the junction of superior venacava and right auricular appendage. It extends downwards along the sulcus terminalis for about 2 cm.

Histology : Muscle fibre are thin, elongated, fusi form, longitudi nally straited and inte rcrossing with one another with a plexiform manner. There is distin ctive cell type known as P cell, which is centrally located and stellate in appearance, related to pace maker activity.

Blood supply :

i. Artery :
Mainly by right coronary and some times from left coronary artery.
ii. Vein : Primitive right great vein, later which become superior venacava.

Nerve supply :

i. Para sympathetic : By right vagus nerve.
ii. Sympathetic : Thoracic 1-5 segment.

Functions :

i. It can initiate the physiological cardiac impulse before any other part of heart.
ii. It is called 'pace maker'.
iii. It can discharge impulse at a rate of about 70-80 impulse/min.

Pace maker : Means regulation of motion. SA node is called pace maker of heart. Because it can initiate normal physiological impulse at first and the rate of discharge is greater than any other part of the heart.

Internodal pathway

It is the pathway that coduct the impulse from the SA node to AV node and left atrium. These internodal tracts contain purkinje type of fibres. Goldman has described three inter nodal pathways-

a. Anterior internodal tract of *Bachman*
b. Middle internodal tract of *Wenckebach*
c. Posterior internodal tract of *Thorel.*

Anterior internodal tract : After coming out from SA node curves round the superior venacava and anterior wall of right atrium it bifurcates into two brances -

i. One knwon as Bachmann's Bundle extends along the dorsal aspect of interatrial band and supplies to left atrium.
ii. Another goes to AV node and merges with other conducting system.

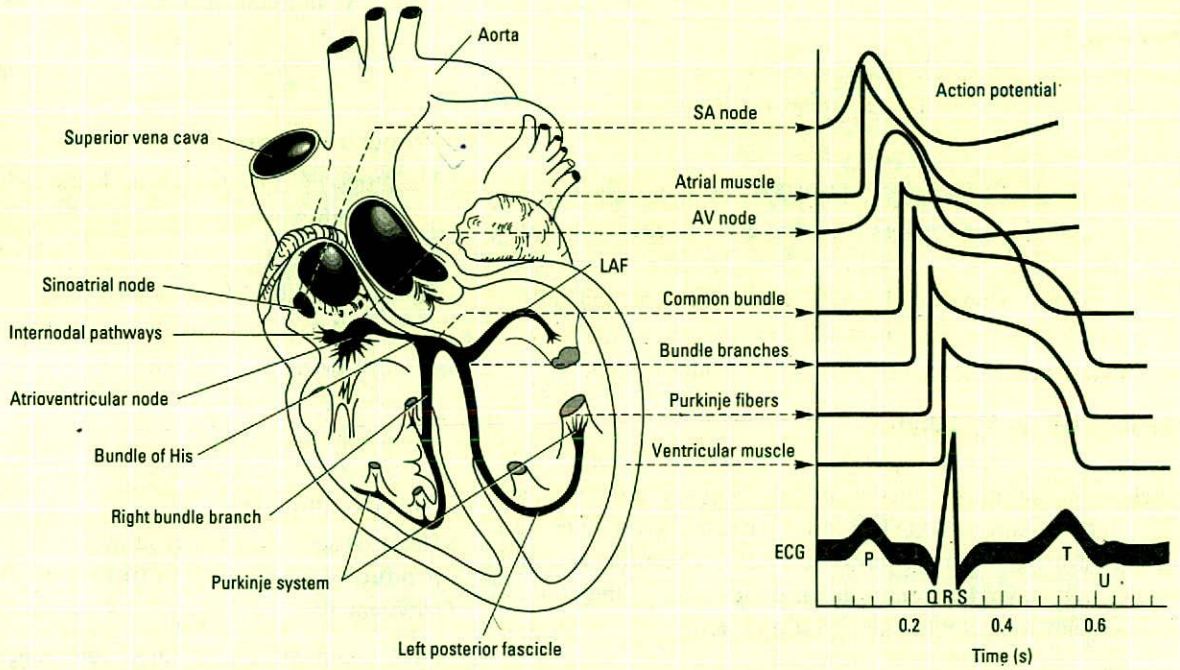


Fig.6-1. *Junctional tissue of the heart.*

Middle internodal tract : Arises from postero- dorsal margin of SA node and grazes the inter atrial septum to reach AV node.

Posterior internodal tract : (Thorel's tract) - Passes along the crista terminalis to reach AV node.

Function :

These internodal tracts serve as preperential pathways for conduction of impulse from SA node to AV node and left atrium.

AV node or Atrioventricular node

Situation : It is situated at the posterior and right border of the interatrial septum near the opening of the coronary sinus.

AV node is normally the only coducting path- way between the atria and the ventricle.

Histology : The cells of AV nodes are cardiac muscle fibre but have a few myofibrils.

Blood supply :

i. Artery : about 90% by right coronary artery and remaining by left coronary artery.
ii. Vein : Into coronary sinus.

Nerve supply :

i. Para sympathetic : Left vagus nerve
ii. Sympathetic : T_1 - T_S sympathetic ganglion.

Functions :

i. It receives impulse originating form SA node and transmit it to the ventricle through the bundle of His at a rate of 0.1 m/sec.
ii. AV node can produce impulse when SA node can fail to produce impulse. So, it is called " reserve pace- maker".
iii. The rate of AV nodal impulse 40-60 impulse/minute.

Bundle of His or AV bundle

Situation : It extends from AV node. It gives off a left bundle branch at the top of the inter ventricular septum and continues as the right bundle branch. The left bundle branch divides into anterior fascicle and a posterior fascicle. The branches and fascicles run subendocardialy down either side of the septum and come into contact with the purkinje system.

Function :

i. *Conductions :* It's main function is to conduct the atrial impulse into ventricle.
ii. *Rhythmicity :* When SA node and AV node fails, the Bundle of His can originate cardiac impulse 30-36 impulse/minute.

Purkinje fiber

It arises from the branches of the Bundle of His, spread from the interventricular septum directly to the papillary muscle and then to the lateral walls of the ventricle ending ultimately with the subendocardial net work. It fibers spread to all parts of the ventricular myocardium.

Functions :

i. To conduct impulso quickly to overy part of ventricular muscle fibre.
ii. It can also initiate impulse in case of atrio-ventricular dissociation at a rate of 15 to 40 impulse/ min.

Cardiac ion channels :

i. *Voltage-gated channels*
   Na^+
   TCa^{++}
   LCa^{++}
   K^+
   Inward rectifying
   Delayed rectifying
   Transient outward
ii. *Ligand-gated K^+ channels* :
   Ca^+ activated
   Na^+ activated
   ATP-sensitive
   Acetylcholine-activated
   Arachidonic acid-activated.

(Ref. Ganong 21th edition, Page 80)

Properties of the heart muscles

The properties of caridac muscle are as follows :

i. Autorhythmicity
ii. Conductivity
iii. Excitability & Contractility
   a. All or none law.
   b. Frank Starling law
iv. Refractory period
v. Tonicity.

Autorhythmicity

Heart muscle does not require any stimulation from outside to produce its impulse (automaticity) at regular intervals (rhythmicity).

Autorhythmicity, also called automaticity. Rhythmicity means that the heart muscle is endowed with the property of generating its own impulse at regular intervals (and these impulses, as will be shown afterwards, can be propagated).

Site of impulse generation : The SAN (sinuatrial node) and the junctional tissues (i.e, the conducting system) can generate the impulses but the working myocardial cells cannot. Normally, however, SAN generates the impulses while other parts of the junctional tissue only propagate the impulse (but does not generate).

Mechanism of sinus nodal rhythmicity : The potential of the sinus nodal fiber between discharges has a negativity of only -55 to -60 millivolts in comparison with -85 to -90 millivolts for the ventricular muscle fiber. The cause of this reduced negativity is that the cell membranes of the sinus fibers are naturally leaky to sodium ions. At this level of negativity, the fast sodium channels have mainly become "inactivated," which means that they have become blocked.

Self-excitation of sinus nodal fibers : Because of the high sodium ion concentration in the extracellular fluid as well as the negative electrical charge inside the resting sinus nodal fibers, the positive sodium ions outside the fibers even normally tend to leak to the inside. Furthermore, the resting nodal fibers

have a moderate number of channels that are already open to the sodium ions. Therefore, influx of positively charged sodium ions causes a rising membrane potential. When it reaches a threshold voltage of about -40 millivolts, the calcium-sodium channels become activated, leading to rapid entry of both calcium and sodium ions, thus causing the action potential. Then the calcium-sodium channels become inactivated (that is, they close) within about 100 to 150 milliseconds after opening, and at about the same time, greatly increased numbers of potassium channels open. Therefore, the influx of calcium and sodium ions through the calcium-sodium channels ceases, while at the same time large quantities of positive potassium ions diffuse out of the fiber, thus terminating the action potential. Furthermore, the potassium channels remain open for another few tenths of a second, carrying a great excess of positive potassium charges out of the cell, which temporarily causes considerable excess negativity inside the fiber; this is called hyperpolarization. This hyperpolarization initially carries the "resting" membrane potential down to about -55 to -60 millivolts at the termination of the action potential.

During the next few tenths of a second after the action potential is over, progressively more and more of the potassium channels begin to close. Now the inward-leaking sodium ions once again over balance the outward flux of potassium ions, which causes the "resting" potential to drift upward once more, finally reaching the threshold level for discharge at a potential of about -40 millivolts. Then the entire process begins again: self-excitation, recovery from the action potential, hyperpolarization after the action potentials is over, drift of the "resting" potential again to threshold, then re-excitation again to elicit another cycle. This process continues indefinitely throughout a person's life.

(Ref. Guyton & Hall-11th Edition; Page 116, 117, 118)

Q. 03. **What is pacemaker potential?**

Ans. Pacemaker potential :

i. *Definition* : Rhythmically dicharging cells have a membrane potential that after each impulse, declines to the firing level. This is called the pace maker potential or pre potential. It triggers the next impulse.

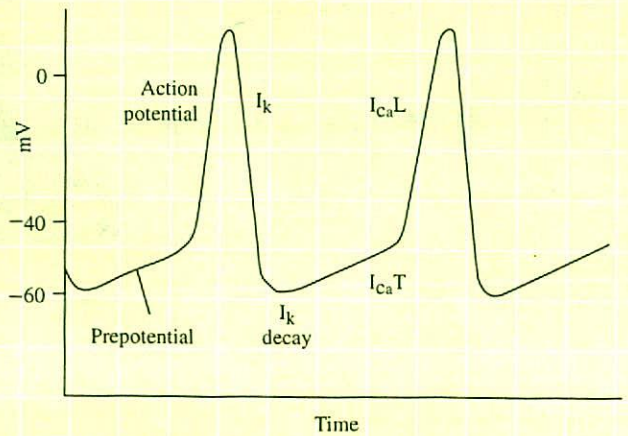


Fig: 6-2. *Rhythmical discharge of a sinus nodal fiber. Also, the sinus nodal action potential is compared with that of a ventricular muscle fiber.*

ii. *Cause* :

a. *First part of the prepotential* : At the peak of each impulse, I_k begins and brings about repolarizanon. I_k then declines, and as K^+ efflux decreases, the membrane begins to depolarize, forming the first part of the prepotential.

b. 2nd part of the prepotential : Ca^{++} channels then open. These are of two types in the heart, the T (for transient) channels and the L (for long-lasting) channels. The calcium current (I_{Ca}) due to opening of T channels completes the prepotential, and I_{Ca} due to opening of L channels produces the impulse. Other ion channels are also involved, and there is evidence that local Ca^{++} release from the sarcoplasmic reticulation (***Ca++ sparks***) occurs during the prepotential.

The action potentials in the SA and AV nodes are largely due to Ca^{++}, with little contribution by Na^+ influx. Consequently there is no sharp, rapid depolarizing spike before the plateau, as there is in other parts of the conduction system and the atrial and ventricular fibers. In addition, prepotentials are normally prominent only in the SA and AV nodes. However, there are 'latent pacemakers' in other portions of the conduction system that can take over when the SA and AV nodes are depressed or conduction from them is blocked. Atrial and ventricular muscle fibers do not have prepotentials, and they discharge spontaneously only when injured or abnormal.

(Ref. Ganong 22th edition; page 548)

Conductivity

Impulse generated from SA node of heart transmit to its epicardial surface through junctional tissue in it.

Q. ***Describe how cardiac impulses is conducted through out the heart?***

Ans. The impulse is originated in the SA node at the rate of 70-80 imp/min. From the SA node the impulse then passes to the AV node through the internodal pathway approximately 0.04 sec. after its oirigin in the SA node. There are three internodal pathway -

i. Anterior.
ii. Middle.
iii. posterior.

The impulse then reaches to the junctional fibres of AV node. From the junctional fibers the impulse reaches to the AV nodal fibers. It takes about 0.06 sec. The impulse then travels through AV nodal fibres to the transitional fibers. There is a delay of about 0.1 second (AV nodal delay) before excitation spreads to ventricle.

From transitional fibers the impulse is transmitted along Bundle if His. The impulse from the Bundle of His passes quickly through the right and left bundle branches.

From the branches of the Bundle of His the impulse quickly passes through the purkinje fibers and spread all over the ventricular muscles.

In human, depolarization of the ventricular muscle starts at the left side of the interventricular septum and moves first to the right across the midportion of the septum. The wave of depolarization then spreads down the septum to the apex of the heart. It returns along the ventricular walls to the AV grooves, proceeding from the endocardial to the epicardial surface. The last part of the heart to be depolarized are the posterobasal portion of the left ventricle, pulmonary conus, and the upper most portion of the septum. *(Pl follow the fig. 6.5)*

(Ref. Guyton 11th ed & Ganong 22th ed; Page-547)

Schematic representation of pathway of impulse in the heart :

SA node

↓

Right atrial muscle | Anterior, middle and posterior internodal pathways | Bachmann's bundle

↓ | ↓ | ↓

AV node | *Left atrial muscle*

↓

His bundle and its branches

↓

Purkinjee fibers

↓

Ventricular muscle.

Excitability & Contractility

Heart muscles responds to a stimulus of adequate strength and duration. The nature of stimulus may be electrical, mechanical or thermal The responds are also electrical, mechanical or thermal.

Excitability : Heart muscle shows excitability, that is, when subjected to a stimulus, it develops a transmembrane action potential (AP). Normally, the SAN regularly generates stimulus → the stimulus is conducted (via conducting tissues) to every single myocardial cell → all such myocardial cells, (because they are excitable), responds by AP.

The resting membrane potential of individual mammalian cardiac muscle cells is about -90 mV (interior negative to exterior). Stimulation produces a propagated action potential that is responsible for initiating contraction.

Depolarization proceeds rapidly, and an overshoot is present, as in skeletal muscle and nerve. But this is followed by a *plateau* before the membrane potential returns to the baseline. In mammalian hearts, depolarization lasts about 2 ms, but the plateau phase and repolarization last 200 ms or more. Repolarization is therefore not complete until the contraction is half over. With extracellular recording, the electrical events include a spike and a later wave that resemble the QRS complex and T wave of the ECG.

As in other excitable tissues, changes in the external K^+ concentration affect the resting membrane potential of cardiac muscle, whereas changes in the external Na^+ concentration affect the magnitude of the action potential.

i. The initial rapid *depolarization* and the overshoot *(phase 0)* are due to opening of voltage-gated Na^+ channels similar to that occurring in nerve and skeletal muscle.

ii. The initial rapid *repolarization (phase 1)* is due to closure of Na^+ channels.

iii. The *subsequent prolonged plateatm (phase 2)* is due to a slower but prolonged opening of voltage-gated Ca^{2+} channels.

iv. Final repolarization *(phase 3)* to the resting membrane potential *(phase 4)* is due to closure of the Ca^{2+} channels and K^+ efflux through various types of K^+ channels.

The voltage-gated Na^+ channel in cardiac muscle has two gates an outer gate that opens at the start of depolarization, at a membrane potential of -70 to -80 mV; and an inner gate that then closes and precludes further influx until the action potential is over (Na^+ channel inactivation).

The slow Ca^{2+} channel is activated at a membrane potential of -30 to -40 mV.

There are three types of K^+ channels that produce repolarization. The *first* produces a transient, early outward

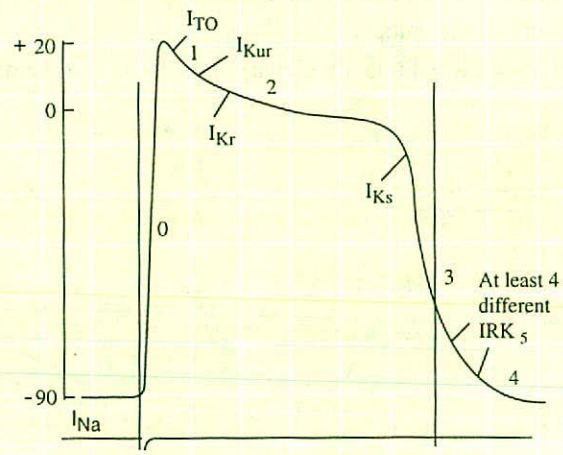


Fig: 6-3. *Phases of the action potential of a cardiac muscle fiber. 0, depolarization due to rapid influx of Na^+ ions; 1, initial rapid repolarization due to closure of Na channels; 2, plateauphase due to slow influx of Na^+ and Ca^{++} through the slow Na^+-Ca^{++} channels; 3, late rapid repolarizaion due to eflux of K^+ ions; 4, base line.*

current (I_{TO}) that produces an early incomplete repolarization. The *second* is inwardly rectifying ie, at plateau potentials it allows K^+ influx but resists K^+ efflux, and only at lower membrane potentials does it permit K^+ efflux. The current it produces is called I_{Kr}. The *third* type is a slowly activating (delayed rectifying) type that produces a current called I_{Ks}. The sum of I_{Kr} and I_{Ks} is a small net outward current that increases with time and *produces repolarization.*

N.B. In cardiac muscle, the repolarization time decreases as the cardiac rate increases.

(Ref. Ganong 22th Edition; Page-78, 80)

The agent which increases the excitability of heart muscle are known as Bathmotropic agent The excitability depends on -

i. Nutrition
ii. O_2 supply
iii. Nerve supply
iv. Optimum concentration of electrolytes.

Contractility : Heart responds the excitation by contraction. This phenomenon occurs due to chemical and mechanical changes in the contractile element- *actin & myosin.* The agent which increases the contractility is called ionotropic agent.The basic mechanical property of the heart muscles is that it can contract. Contraction may or may not cause, shortening. Neverthless, all contractions generate force and produce squeeze on the blood in ventricular or atrial cavities → which in turn, ultimately speaking, causes ejection of blood from these cavities.

When free Ca^{++} ions are available in sufficient concentration within the WMC (or SMC), the Ca^{++} ions bind with the troponin C.

This results in some physiochemical change in the (resting) actin tropomyosin complex, so that tropomyosin loosens → nextly the tropomyosin moves away from the actin → the myosin head binding sites of actin are uncovered.

Nextly, the globular head of myosin attaches with the actin, and this constitutes the cross bridge → swivelling action → movement of actin → shortening.

In relaxed state, the free (Ca^{++}) in the ICF is so low that the tropomyosin continues to cover the active sites of the thin filament.

After the end of a contraction, the ICF free Ca^{++} concentration falls again (relaxation develops).

a. ***All or none law*** : If an adequate stimulus is applied to heart muscle, the heart muscle responds to its maximum, but if the stimulus is not adequate it does not responds at all.

In 1871, Bowditch discovered this law, which, in short, is : apply a thrsehold stimulus (= a stimulus which is just sufficient, neither excess nor less), to the heart, the heart contracts. Now, apply a stronger stimulus. Heart contracts but force of this contraction is not more than that created by the threshold stimulus. Conclusion is, by increasing the strength of stimulus, the force of contraction cannot be increased. So far as the strength of stimulus is concerned heart therefore shows, all or none law, i.e., it contracts with requisite force (when the stimulus is adequate) or does not contract at all (when it is below adequate). (Force of contraction, as stated above, can be changed only by via Frank Starling's law or by changing its inotropic state).

b. ***Frank Starling law*** : Within the physiological limit the greater the length of cardiac muscle fibre the greater will be the force of contraction.

Within physiological limit, greater the end diastolic fibre length of the myocardium (ie greater the end diastolic volume), greater is the force of contraction.

Importance of Frank-Starling's law :

1. *This law ensures that output per stroke of one ventricle is the same in the other ventricle. Thus it can readily be seen that it is a life saving device* : Suppose, the right ventricular output per stroke is slightly greater than that of the left. This will cause accumulation of blood in the left ventricle. But because of the presence of the Frank-Starlingís law, as the blood accumulates, the Frank-Starlingís law begins to operate → more complete evacuation of the left ventricle → the two ventricles now will have the same output again. Lack of presence of this law, then, would have produced a catastroke (accumulation of blood in the pulmonary circulation → pulmonary edema).
2. *Frank-Starling's law is a life saving device in cardiac failure* : Suppose, there is left ventricular failure (LVF) due to insufficiency of contraction of the left ventricle → accumulatiom of blood within the left ventricle and lack of blood supply to the vital organs like brain (which can kill the patient) → accumulation of blood in the ventricle leads to operation of the Frank Starling's law → greater cardiac output → satisfactory supply to the vital organs. In LVF, therefore, the contractility of the left ventricular muscle is poor, but this is compensated by the operation of Frank Starling's law.

Q. 04. **Briefly explain the causation of plateau.**

Ans. *Causation of plateau* :

i. The prolonged plateau *(phase 2)* is due to a slower but prolonged opening of voltage-gated Ca^{++} channels. The slow Ca^{++} channel is activated at a membrane potential of -30 to -40 mV. Ca^{++} channels allow diffusion of mainly of Ca^{++} but of some Na^+ ions as well.
ii. A second factor sometimes partly responsible for the plateau

is that the voltage-gated K^+ channels are even slower than usual to open, often not opening greatly until the very end of the plateau. This delays the return of the membrane potential toward the resting value.

(Ref. Guyton 10th Edition; Page-66)

Factors influencing myocardial contractility

Ans. Factors influencing myocardial contractility are :

I. *Positively inotropic effect exerted by* :
   i. *Sympathetic nerves* : The whole length-tension curve shifts upward and to the left
   ii. *Catecholamines* exert their inotropic effect : *Norepinephrine and epincphrine* : The positively inotropic effect of the norepinephrine liberated at the nerve endings is augmented by circulating norepinephrine, and epincphrine has a similar effect.
   iii. *Xanthines* such as *caffeine* and *theophylline* that inhibit the breakdown of cAMP are positively inotropic.
   iv. *Digitalis and related drugs*
   vi. *Glucagon* which increases the formation of cAMP, is positively inotropic, and it has been recommended for use in the treatment of some heart diseases
   vi. *Changes in cardiac rate and rhythm* also affect myocardial contractility : myocardial contractility increases as the heart rate increases
   viii. *Intracellular* Ca^{++} : Next succeeding contraction is stronger than the preceding normal contraction.

II. *Negatively inotropic effect exerted by* :
   i. Parasympathetic nerves : There is a negatively inotropic effect of *vagal stimulation* on the atrial muscle and a small negatively inotropic effect on the ventricular muscle.
   ii. Hypercapnia, hypoxia, acidosis, drugs such as quinidine, procainamide, and barbiturates depress myocardial contractility.

(Ref. Ganong 22th ed; Page-575, 576)

Q. 00. **What is ionotropic effect?**

a. *Definition* : Alteration of the force of contraction of the heart is termed as ionotropic effect.

b. *Type* :
   i. Positive inotropic effect
   ii. Negative inotropic effect.

Positively inotropic effect exerted by :
   i. Sympathetic nerves
   ii. Catecholamines i.e orepinephrine and epincphrine
   iii. Xanthines such as caffeine and theophylline
   iv. Digitalis and related drugs
   vi. Glucagon
   vi. Changes in cardiac rate and rhythm
   vii.. Intracellular Ca^{++}.

Negatively inotropic effect exerted by :
   i. Parasympathetic nerves
   ii. Hypercapnia
   iii. Hypoxia
   iv. Acidosis
   v. Drugs such as quinidine, procainamide, and barbiturates.

Q. 00. **What is chronotropic effect?**

a. *Definition* : Any alteration of the heart rate by nervous stimulation or drugs is termed as chrono- tropic effect.

b. *Type* :
   I. *Positive chronotropic action* : Means an increase in the heart rate.
   Cause :
      i. Sympathetic stimulation
      ii. Adrenergic drugs i.e adrenaline, noradre- naline
      iii. Anticholenergic drugs i.e atropine.
   II. *Negative chronotropic action.*: Means a decrease in the heart rate.
   Cause :
      i. Parasympathetic stimulation
      ii. Drugs : adrenergic antagonist i.e reserpine, ergotamine etc.

Role of Ca^{++} ions in cardiac action potential

i. Ca^{++} is the current carrying ion in pacemaker tissues- thus produces depolarization in pacemaker tissues.
ii. Ca^{++} is responsible for cardiac action potential (in skeletal muscle and axon Ca^{++} is not involved in action potential).
iii. The involvment of Ca^{++} conductance in cardiac muscle is responsible for the long duration of the cardiac action potential (about 250 ms) copared with only a few milliseconds in skeletal muscle and axon.
iv. The force of myocardial contraction (ionotropic effects) is regulated by influx of Ca^{++} into myocytes.

Refractory period

It is the period during which heart muscle is nonresponsive to external stimuli or restimuli. Refractory period of heart is 0.30 sec. Refractory period is of two types :

i. Absolute refractory period
ii. Relative refractory period.

1. ***Absolute refractory period :*** It is the period of conduction during which heart muscle is refractory to a restimulus.
   The whole depolarization and first one third of repolarization is absolute refractory period. It is about 0.25 second.

2. ***Relative refractory period :*** It is the period of conduction during which heart muscle responds a slight to a very

strong stimulus. The last two third of the repolariztion is relative refractory period. It is about 0.05 sec.

Significance :

i. Heart muscle can not be tetanized.
ii. Heart muscle can not be fatigued.
iii. Ensures enough time for recovery of cardic muscle by getting nutrition and O_2 supply.

During this refractive period heart muscle ensure enough time for recovery by getting nutrition and O_2 supply. For this reason heart muscle is not tetanized or fatigued.

Tonicity

It is state of partial contraction of the heart muscle over the contained blood.

Q. ***What is "pace maker" ? Why SA node is called so?***

Ans. *Pace maker* :

Definition : The general meaning of pace maker is that the rider or runner who sets the pace of the race.

SA node is called the pace maker. It produces 70-80 impulse/minute, which coincides with heart rate.

SA node is called pace maker as :

i. It originates the impulses at first.
ii. It maintains the normal cardiac rhythm.
iii. The rate and rhythm originated by SA node is higher than that of all.

Q. ***Prove that SA node is the pace maker of heart ?***

Ans : Evidences -

1. Its destruction or removal causes cessation of atrial contraction.
2. In high temparature, the SA node is heated so, the rate of heart is increased, selective heating or cooling of this part hasten's or slow's the rate of heart.
3. SA node is first part of heart to show electronegativity.
4. In tissue culture, the pace maker tissues are first to show activity.

Q. ***Why does the SA node control the heart's rhythmicity rather than AV node or Purkinje fibre ?***

Ans. The discharge rate of SA node is much more greater than either AV node or Purkinje fibers. Each time the sinus node discharges, its impulse is conducted into both the AV node & purkinje fibers, discharging their excitable membrane. But the sinus node loses it hyperpolarization much more rapidly than does either of the other two and emits a new impulse before either one of them can reach its own thresold for self excitation. The new impulse again discharges both the AV node and purkinje fibres. This process continue on and on. Thus the SA node controls the beat of heart.

(Ref. Guyton & Hall-11th edition)

Q. ***Describe the velocity of conduction and the rate of impulse generation of heart muscles.***

Ans.

Tissue	*Volocity of conduction. (Meter/second)*	*Rate of impulse generation (Impulse/minute)*
SA node	0.05	70 - 80
AV node	0.05	40 - 60
Bundleof His	*1*	*30 - 36*
Purkinje fiber system	*4*	*15 - 40*
Atrial pathway	*1*	*60*
Atrial muscle	0.3	-
Ventricular muscle	1	20 - 40
	(Ref. Ganong 22th edition)	*(Ref. Guyton 11th edition)*

Q. ***Describe the rate and time taken by impulses to conduct from SA node to heart muscles.***

Ans.

1. From SA node to atrial muscle	: 0.03 second.
2. From SA node to AV node through internodal pathway	: 0.03 second.
3. AV node itself before enters to penetrating portion of AV bundle	: 0.09 second.
4. Penetrating portion of AV bundle	: 0.04 second.
**SA node up to distal portion of AV bundle i.e. from atria to ventricle (.03 +.09 +.04 sec)*	*: 0.16* second.
5. Distal portion of AV bundle to termination of purkinje fiber (i.e up to one third of ventricular muscle)	: 0.03 second.
6. From endocardial surface to epicardial surface of the ventricle	: 0.03 second.
** Initial bundle branches to the last of the ventricular fibers (0.03 + 0.03)*	*: 0.06 second.*

Note: Purkinje fiber leads from AV node through AV bundle into the one third of ventricular muscles.

(Ref. Guyton & Hall-11th ed; Page 116, 117, 118)

Reserve Pace Maker

When the SA node fails to generate impulse then the AV node become the pace maker and produces impulse at its own rate of 40-60 impulse/min. So it is called reserve pace maker. Then the heart contracts at a rate of 40-60/minute.

(Ref. Guyton 11th ed; Page-120)

Ectopic Pace Maker

A pace maker elsewhere than SA node is called ectopic pace maker. Obviously, an ectopic pace maker causes an abnormal sequence of contraction of different part of heart.This often occurs inthe AV node or in purkinje fibers. Under rare conditions a point in the atrial or ventricular muscle develops excessive excitability and becomes the pace-maker.

(Ref. Guyton 11th ed; Page-120)

AV nodal delay

AV node is responsible for the delay in transmission of impulse generated in the SA node. This delay in impulse transmission is called AV nodal delay. It is about 0.09 sec.

Causes of AV nodal delay :

i. Junctional fibres of the AV node are very small in size.
ii. Resting membrane potetials of these fibres are much less negative than the normal resting membrane potential of other cardiac muscle.
iii. Very few gap junctions connect the successive fibres in the pathway, so that there is great resitance to the conduction of excitatory ions from one fibre to the next.
iv. Prolonged refractory period of AV node.

Importance of AV nodal delay : AV nodal delay allows time for the atria to empty their content into the ventricles before the ventricular contraction begins.

(Ref. Guyton 11th edition; page 118)

Idioventricular rhythm of cell

If impulses generated in SA node fails to reach AV node, the AV node generates impulse for the rest of the heart at a rate of about 40 -60 impulse/min. This is called idioventricular rhythm of cell.

Stokes Adams syndrome

When AV block occurs that is, when the cardiac impulse fails to pass from the atria into the ventricles through the AV nodal and bundle system - the atria continue to beat at the normal rate of rhythm of the sinus node, while a new pacemaker develops in the purkinje system of the ventricles and drives the ventricular muscle at a new rate somewhere between 15 and 40 beats per minute. After a sudden block, the Purkinje system does not begin to emit its rhythmical impulses until 5 to 30 seconds later because, before the blockage, the Purkinje fibers had been "overdriven" by the rapid sinus impulses and, consequently, are in a suppressed state. During these 5 to 30 seconds, the ventricles fail to pump blood, and the person faints after the first 4 to 5 seconds because of lack of blood flow to the brain. This delayed pickup of the heart beat is called Stokes Adams syndrome. If the delay period is too long it can lead to death.

(Ref. Guyton 11th ed; Page-121)

Ventricular escape

Stimulation of the vagus nerve decreases the rate and rhythm of SA node and also decreases the excitability of AV junctional fibres there by slowing transmission of cardiac impulse into ventricle.

Very strong stimulation of the vagi can completely stop the rhythmic contraction of SA node or completely block transmission of cardiac impulse through the AV junction. As a result, the ventricles stop beating for 4 to 10 sec. But then some point in purkinje fibers, usually in the ventricular septal porton of the AV bundle develops rhythm of it's own and causes ventricular contraction at a rate of 15-40 beats per minute. This is called ventricular escape.

(Ref. Guyton& Hall-11th edition; Page-121)

Cardiac Cycle

Definition : The cardiac events that occur from the begining of one heart beat to the begining of the next are called the cardiac cycle. ***or***

(Ref. Guyton & Hall-11th edition; Page 106)

The sequence of events that occur in heart in each beat with contraction and relaxation is called cardiac cycle. ***or***

The cyclic repeatation of the various changes in heart from beat to beat, is called cardiac cycle.

Cardiac cycle time

The time taken for one complete cardiac cycle to occur with a normal heart rate.

If the normal heart rate = 75

The cardiac cycle time will be $= \frac{60}{75}$ second.

$= 0.8$ second.

The cardiac cyclle time will be inversely proportional to the heart rate.

Law of cardiac cycle

1. Ventricular systole and diastole does not overlaped by each other.
2. Similarly atrial systole and diastole does not overlaped by each other.
3. Atrial systole is overlaped by the ventricular diastole.
4. Atrial systole coincides with last rapid filling phase.
5. Cardiac cycle time is inversely proportional to heart rate.

Systole

The period of contraction of heart is called cardiac systole or systole.

(Ref. Guyton & Hall-11th Edition; page 106)

Diastole

The period of relaxation of heart is called cardiac diastole or diastole.

The cardiac cycle consist of a systole and diastole.

(Ref. Guyton & Hall-11th Edition; page 106)

Events of cardiac cycle

In Atria :

1. *Atrial systole* : 0.1 second.
2. *Atrial diastole* : 0.7 second.

In Ventricle :

1. *Ventricular systole* : 0.3 second.
   a. Isovolumetric (Isometric) contraction phase : 0.02 to 0.03 second (0.05 second, *Ganong 21th Edition*).
   b. Rapid ejection phase
   c. Reduced ejection phase
2. *Ventricular diastole* : 0.5 second.
   a. Protodiastolic phase : 0.04 second.
   b. Isometric (volumetric) relaxation phase : 0.03 to 0.06 second.
   c. First rapid filling phase
   d. Slow filling phase — 0.4 sec
   e. Last rapid filling phase.

Atrial Systole : It initiates the cardiac cycle as the pace maker (SA node) is in the atria. Contraction of atria propels some additional blood into the ventricles (about 30%). Contraction of the atrial muscle that surrounds the orifices of the superior and inferior vena cava and pulmonary veins narrows their orifices and the inertia of the blood moving towards the heart tends to keep blood in it. However, there is some regurgitation of blood into the veins during atrial systole. About 30% of ventricular filling occurs actively during atrial diastole.

(Ref. Ganong 22th edition; Page 565)

Atrial Diastole : At the end of atrial systole atrial diastole occurs and during this period blood enters into atria from great veins. Its duration is about 0.7 sec. About 70% of ventricular filling occurs passively during atrial diastole.

(Ref. Ganong 22th edition; Page 565)

Ventricular Systole : It starts at the end of atrial systole and lasts for 0.3 second. At the onset of ventricular systole A-V valve closes and produces 1st heart sound. It has following phases-

a. ***Isovolumic or isometric contraction phase*** *:* (Iso= same, metric= lenght) In this phase muscle does not shorten (this is not strictly true because there is apex-to-base shorting and circumferetial elongation.) but the tension increases which is called isometric contraction. At the begining of the ventricular systole (there is a brife period during which) both valves (AV and semilunar) remain closed and the ventricle contracts as a closed cavity. It is called *isometric contraction phase*. This period of isovolumetric contraction lasts about 0.02 to 0.03 second (0.05 second, *Ganong 20th ed*), until the pressures in the left and right ventricles exceed the pressure in the aorta (80 mm of Hg) and pulmonary artery (10 mm of Hg) and the aortic and pulmonary valves open. During isovolumetric contraction, the AV valves bulge into the atria, causing a small but sharp rise in atrial pressure. In this period no blood passes out. It is marked at the onset by the closure of AV valve and its termination by the opening of semilunar valve.

(Ref. Guyton 11th ed; P-108 and Ganong 22th ed; P-565)

b. ***Ejection phase*** *:* During isometric contraction phase the pressure within the ventricle sharply rises and semilunar valve opens. The intraventricular pressure rises to a maximum and then declines somewhat before ventricular systole ends. Peak left ventricular pressure is about 120 mm of Hg, and peak right ventricular pressure is about 25 mm of Hg or less . It has two parts-

   i. *Rapid ejection phase :* It is 1st third of ejection phase during which out flow is about 70% .

   ii. *Slow ejection phase :* It is the last third of ejection phase during which out flow is minimum about 30%.

(Ref. Guyton 11th ed; P-108 and Ganong 22th ed; P-565)

Ventricular Diastole : It starts at the end of ventricular systole and lasts for 0.5 second. Its has following phases -

a. *Protodiastolic phase :* It is the interval between the onset of diastole and closure of semilunar valve. As the diastole starts the pressure in the ventricles falls and after a short interval semilunar valve is closed by the high pressure in aorta. *It produces 2nd heart sound. Duration* : 0.04 second.

b. *Isometric relaxation phase* : It is the interval between the closure of semilunar valve and opening of A-V valve. In this phase both A.V and semilunar valve remain close & the ventricle relaxes at a closed cavity. No blood enters into the ventricle in this phase and there is sharp fall of intraventricular pressure. *Duration :* 0.06 second (0.03-0.06 second).

c. *Filling phase* : At the end of isometric relaxation phase the ventricular pressure falls and AV valve open due to high pressure in atria. Then blood enters into ventricle and ventricular filling phase begins at a ventricular volume of about 45 ml and a diastolic pressure near 0 mm Hg and with the volume increasing to 115 ml and the diastolic pressure rising to about 5 mm Hg.

(Ref. Guyton & Hall-11th edition; page 108)

It has following phase-

   i. *1st rapid filling phase :* It is the 1st part of filling phase. At this phase the intraventricular pressure marked fall and inflow of blood become more intense. So, blood rushes from atria to ventricle and 3rd heart sound will be produced. *Duration :* 1st third of diastole.

   ii. *Slow filling phase :* The amount of filling in this period is minimum.

The filling is slow as :

a. Ventricle already filled with large extent
b. The ventricular pressure slowly rises
c. The valve remains flattering condition.

Duration : Middle third of diastole.

iii. *Last rapid filling phase :* Here ventricular diastole coincides with atrial systole. Due to atrial contraction blood rushes into the ventricle in this phase and produce 4th heart sound. *Duration :* Last third of diastole.

Total filling time : 0.4 second.

(Ref. Guyton 11th ed; P-108 and Ganong 22th ed; P-565 and others)

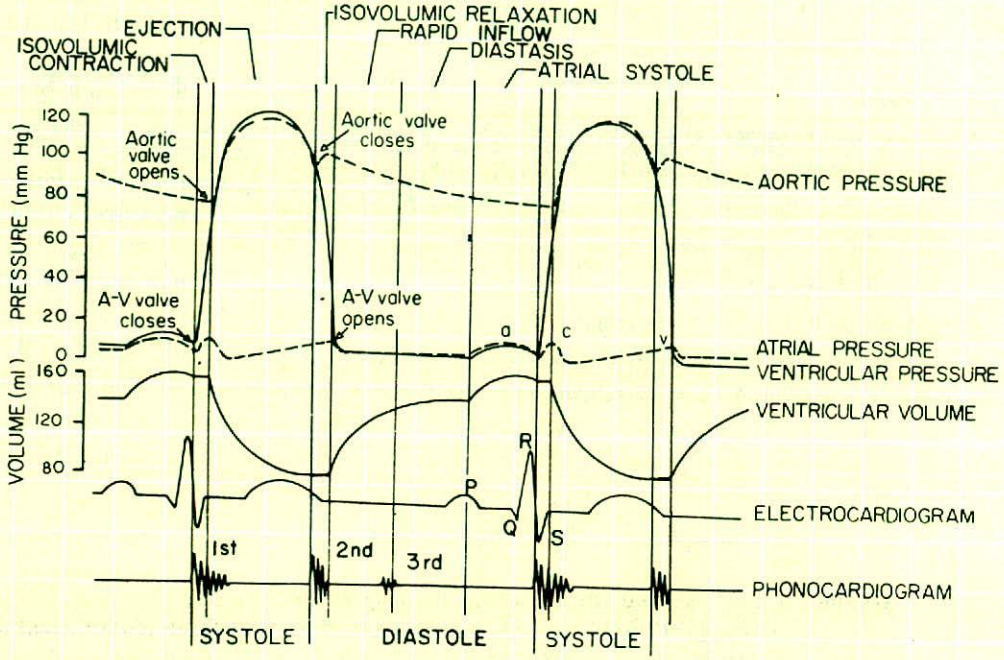


Fig. 6-4. *Events of the cardiac cycle for left ventricular function, showing changes in left atrial pressure, left ventricular pressure, aortic pressure, ventricular volume, the electrocardiogram, and the phonocardiogram.*

Pressure changes during cardiac cycle

Prssure in aorta and right & left ventricles in systole & diastole :

	Aorta (mm Hg)	*Left ventricle (mm Hg)*	*Right ventricle (mm Hg)*
Systole	*120*	*120*	*25*
Diastole	*80*	*0 - 5*	*0*

(Ref. Ganong-22th edition; Guyton 11th edition)

Prssure changes during cardiac cycle :

1. Right atrium : 0-8 mm of Hg
2. Left atrium : 4-12 mm of Hg
3. Right ventricle :
   a. During systole : 15-30 mm of Hg
   b. During diastole : 0-5 mm of Hg
4. Left ventricle :
   a. During systole : 90-140 mm of Hg
   b. During diastole : 04-12 mm of Hg
5. Pulmonary artery :
   a. During systole : 15-30 mm of Hg
   b. During diastole : 05-15 mm of Hg
6. Aorta :
   a. During systole : 90-140 mm of Hg
   b. During diastole : 60-90 mm of Hg

(Ref. Davidson's Medicine)

Relationship of the electrocardiogram to the cardiac cycle

The electrocardiogram shows the P, Q, R, S, and T waves, which are discussed later. They are electrical voltages generated by the heart and recorded by the electrocardiograph from the surface of the body.

The *P wave* is caused by spread of depolarization through the atria, and this *is followed by atrial contraction*, which causes a slight rise in the atrial pressure curve immediately after the P wave. About 0.16 second after the onset of the P wave, the *QRS waves* appear as a result of depolarization of the ventricles, which *initiates contraction of the ventricles* and causes the ventricular pressure to begin rising. Therefore, the QRS complex begins slightly before the onset of ventricular systole.

Finally, one observes the ventricular T wave in the electrocardiogram. This represents the stage of repolarization of the ventricles, at which time the ventricular muscle fibers begin to relax. Therefore, the *T wave* occurs *slightly before the end of ventricular contraction.*

(Ref. Guyton & Hall-11th edition; Page-107)

Changes takes place during cardiac cycle

The changes associated with cardiac cycle are as follows :

1. *Changes in pressure* :
   i. Intraventricular pressure change.
   ii. Intra atrial pressure change.

iii. Pressure change within aorta.
iv. Pressure changes within pulmonary artery.

2. Changes in volume :
   i. Atrial volume change
   ii. Ventricular volume change
3. *Production of heart sound and apex beat.*
4. *Production of pulse and appearance of pulse wave.*
5. Electrical change.
6. *Electro-cardiogram (ECG) changes.*
7. *Systemic, Pulmonary and coronary circulation changes.*

Discussion

A. ***Intra venricular pressuse changes***
   a. *During ventricular systole :*
      1. In isometric contraction period, intraven-tricular pressure sharply rises as ventricule contracts in a closed cavity due to closure of both AV and SL valve.
      2. In maximum ejection phase, since blood passes out pressure should fall in ventricle. But the force of contraction is stronger than out flow, so intraventricular pressure rises.
      3. In reduced ejection phase, force of contrac-tion is less than out flow so intraventricular pressure gradually fall.
   b. *During ventricular diastole :*
      1. In protodiastolic phase pressure continue to fall.
      2. In isometric relaxation phase pressure sharply fall until AV valve open because ventricle relax in a closed cavity.
      3. In first rapid filling phase, though blood rushes into ventricle but pressure slowly falls because rate of relaxation is stronger than filling.
      4. In last rapid filling phase, corresponds with atrial systole, blood pumps into ventricle and pressure suddenly rises.

B. ***Intra atrial pressure changes*** :
   a. During atrial systole, pressure sharply rises and causes first positive curve or a wave.
   b. During atrial diastole, pressure should fall in atria. But instead that, pressure sharply rises due to bulging of AV valve and backward flow of blood towards atria caused by isometric contraction phase. It causes c wave.
   c. Then pressure sharply fall because atria continue to relax and AV valve regained its position.
   d. At the later part of ventricular systole, intra atrial pressure rise and causes V wave.

C. ***Pressure change in aorta***
   1. In isometric contraction phase, slight aortic pressure rises due to bulging of SL valve towards aorta.
   2. When SL valve opens, blood enters into aorta and aortic pressure smoothly rises and falls running parallel with ventricular pressure.
   3. During diastole, pressure fall due to backward flow of aortic blood towards ventrcle.
   4. Then pressure slowly fall because blood passes to the periphery.

D. **Volume changes** :

End diastolic ventricular volume	: About 130 ml
End systolic ventricular volume	: About 50 ml

(Ref. Ganong 22th edition; Page-565)

End diastolic ventricular volume	: 110-120 ml
End systolic ventricular volume	: 40-50 ml

(Ref. Guyton Hall-11th edition; Page-108)

E. **Production of heart sound** :
   a. *1st heart sound :* Sudden closure of AV valve at the onset of ventricular systole.
   b. *2nd heart sound :* Closure of semilunar valves (aortic and pulmonary valves) just after the end of ventricular systole).
   c. *3rd heart sound :* Due to vibrations set up by the inrush of blood from atria to ventricle during the 1st rapid filling phase of ventricular diastole.
   d. *4th heart sound :* Due to inrush of blood from atria to ventricle during last rapid filling phase of ventricular diastole by atrial contraction.

Q. ***Why minimum pressure exist in arterial system during diastole?***

Ans. During systole the propulsive force of heart cause the systolic pressure but during diastole such propulsive force is absent. For this reason minimum pressure exist in the arterial system during diastole.

Actually the pressure would fall to a very low level but such does not happen due to the elastic recoil of the arteries.

Heart Sound

Definition : The vibratory motion of heart produced during the different events of cardiac cycle conducts through the structure surrounding the heart and produces special audible sound called heart sound.

Causes of heart sound

i. Vibration of the taut valves immediately after closure.
ii. Vibration of the adjacent blood.
iii. Vibration of the walls of the heart and major vessels around the heart.

(Ref. Guyton& Hall-11th edition; Page-269)

Classification of heart sound

Heart sound is classified into four in number :

i. 1st heart sound.

ii. Second heart sound.

iii. 3rd heart sound.

iv. 4th heart sound.

1st and 2nd heart sound is audible by stethoscope, 3rd and 4th heart sound is detected by phonocardiograph.

First heart sound

It is a low, slightly prolonged 'lub' (*first sound*), caused by vibrations set up by the sudden closure of the mitral and tricuspid valves at the start of ventricular systole.

Duration : About 0.15 second.

Fequency : 25-45 Hz.

It is soft when the heart rate is low, because the ventricles are well filled with blood and the leaflets of the AV valves float together before systole.

(Ref. Ganong 22th edition; Page 569)

Procedure of causes of first heart sound : In generating the first heart sound, contraction of the ventricles first causes sudden backflow of blood against the A-V valves (the tricuspid and mitral valves), causing them to close and bulge toward the atria until the chordae tendineae abrupty stop the backbulging. The elastic tautness of the chordae tendineae and of the valves then causes the backsurging blood to bounce forward again into each respective ventricle. This sets the blood and the ventricular walls as well as the taut valves into vibration and causes vibrating turbulence in the blood. The vibrations travel through the adjacent tissues to the chest wall, where they can be heard as sound by the stethoscope.

(Ref. Guyton 11th ed; Page 269)

Causes of loudness of 1st heart sound :

1. *Vigor of ventricular contraction :* Increased Sympathetic supply increases the myocardial contractility, the rate of change in ventricular pressure is increases, and a louder Ist heart sound may heard.
2. *The stiffness of ventricle and valve structures :* With fibrosis, the AV valves become stiffer, leading to a sound that is louder and some what higher in frequency then normal.
3. *The position of mitral valves leaflets at the begining of ventricular systole :* At the time of ventricular systole the mitral valve is widely open, by the time the valve closes, a significant amount of blood moving towards the valve and producing a noisy sound.
4. *P-R. interval :* It is the time between the atrial and ventricular exitation If P-R interval is shorter than normal the AV valve will be open at the onset of ventricular systole, So that when they finally are closed, the sound is louder than normal.

(Ref. Selkurt 5th page - 232)

Second heart sound

It is a shorter, high-pitched 'dup' (*second sound*), caused by vibrations associated with closure of the aortic and pulmonary valves just after the end of ventricular systole.

Duration : About 0.12 second.

Frequency : 50 Hz.

It is loud and sharp when the diastolic pressure in the aorta or pulmonary artery is elevated, causing the respective valves to shut briskly at the end of systole.

The interval between aortic and pulmonary valve closure during inspiration is frequently long enough for the second sound to be reduplicated (*physiologic splitting of the second sound*). Splitting also occurs in various diseases.

(Ref. Ganong 22th edition; Page-569)

Procedure of causes of second heart sound : The second heart sound results from sudden closure of the semilunar valves. When the semilunar valves close, they bulge backward toward the ventricles, and their elastic stretch recoils the blood back into the arteries, which causes a short period of reverberation of blood back and forth between the walls of the arteries and the semilunar valves, as well as between these valves and the ventricular walls. The vibrations occurring in the arterial walls are then transmitted mainly along the arteries. When the vibrations of the vessels or ventricles come into contact with a 'sounding board,' such as the chest wall, they create sound that can be heard.

(Ref. Guyton 11th edition; Page 269)

Third heart sound

A soft, low-pitched *third sound* is heard about one-third of the way through diastole in many normal young individuals. It coincides with the period of rapid ventricular filling and is probably due to vibrations set up by the inrush of blood.

Duration : The third sound has a duration of 0.1 second.

(Ref. Ganong 22th ed; Page 569)

Fourth heart sound

It can sometimes be heard immediately before the first sound when atrial pressure is high or the ventricle is stiff in conditions such as ventricular hypertrophy. It is due to ventricular filling and is rarely heard in normal adults.

(Ref. Ganong 22th ed; Page 569)

Q. ***Why 2nd heart sound has shorter duration than the 1st sound?***

Ans. *First sound* is caused by vibrations set up by the sudden closure of the mitral and tricuspid valves at the start of ventricular systole and the *second sound* is caused by vibrations associated with closure of the aortic and pulmonary valves just after the end of ventricular systole.

The reason for the shorter second sound is that the semilunar

valves are more taut than the A-V valves, so that they vibrate for a shorter period than do the A-V valves.

(Ref. Guyton & Hall-11th edition; Page 269)

Q. ***Why 1st heart sound has longer duration than the 2nd sound?***

Ans. *First sound* is caused by vibrations set up by the sudden closure of the mitral and tricuspid valves at the start of ventricular systole and the *second sound* is caused by vibrations associated with closure of the aortic and pulmonary valves just after the end of ventricular systole.

Semilunar valves are more taut than the A-V valves. The A-V valves vibrate for a longer period than do the semilunar valves. So the 1st heart sound has longer duration than the 2nd sound.

(Ref. Guyton & Hall-11th edition; Page 269)

Q. ***Why 2nd heart sound has a higher frequency than 1st sound?***

Ans. The second heart sound normaly has a higher frequency than the first heart sound for two reasons :

1. Because of the tautness of semilunar valves in comparison with much less taught AV valve.
2. Because of the greater elasticity coefficient of the arteries that provide the principal vibratring chambers for the second heart sound in comparison with the much losser vetricular chambers that provide the vibrating system for the 1st heart sound .

(Ref. Guyton & Hall-11th edition; Page 269)

Q. **Name the sites, where the heart sounds are best heard.**

Ans. There are four different areas on the chest wall where the heart sounds are best heard are given below :

i. *Mitral area :* On the apex beat, in the left 5th intercostal space, 9 cm from the midsternal line.

ii. *Tricuspid area :* Over the left border of the sternum in the left 4th intercostal space.

iii. *Aortic area :* At the right border of the sternum in the right 2nd intercostal space.

iv. *Pulmonary area :* At the left 2nd inter costal space, at the margin of the sternal border.

Clinical importance of heart sounds

The 1st and 2nd heart sound is normally heard through a stethoscope. The quality, character, and timing of these sounds may be altered in various cardiac diseases. So, 1st and 2nd heart sounds are important in :

i. Diagnosis of valvular heart diseases :
   a. Mitral stenosis : Loud 1st heart sound
   b. Calcified mitral valve : Soft 1st heart sound
   c. Aortic stenosis : Reversed splitting 2nd heart sound.

ii. Diagnosis of cardiodynamics status :
   a. Hyper dynamic condition : Loud 1st and 2nd heart sound

iii. Diagnosis of conduction defect :
   a. Bundle branch block : Wide physiological splitting of 2nd heart sound.

iv. Diagnosis of congenital heart disease.

v. Differentiating the murmur whether it is systolic or diastolic in origin.

Q. 04. **Name the clinically audible *(abnormal)* heart sounds with their significance.**

Ans. *Abnormal heart sounds are* : In addition to normal heart sounds, abnormal sounds may be produced during cardiac cycle due to abnormalities in cardiac
valves or abnormal blood flow and pressure gradients. Some abnormal sounds are :

i. Murmurs
ii. Gallop rhythm
iii. Pericardial friction rub
iv. Ejection click
v. Bruits.

i. Murmurs : Are produced by turbulent blood flow through an abnormal valve or high blood flow through a normal valve.
   Character : Murmurs are high frequency sounds and are often described as blowing in quality.
   Significance : Valvular stenosis, valvular incompetence.

ii. Gallop rhythm : The presence of a third or fourth heart sound produces a triple rhythm that, when associated with sinus tachycardia, sounds like a galloping horse- a *gallop rhythm*. The cadence of a gallop rhythm due to third heart sound has been lined to 'Kentucky' whilst that due to a fourth heart sound resembles 'Tennessee'.

ii. Pericardial friction rub : A pericardial friction rub is a scratching or crunching noise produced by the movement of inflamed pericardium. Since it is high frequency, it is best heard with the diaphragm of stethoscope. This is an extra cardiac sound.

iii. Ejection click : An ejection click sound occurs immediately following the first heart sound. The sudden opening of a deformed but mobile aortic or pulmonary valve produces the ejection click.

iv. Bruits : Are murmurs arising from a peripheral artery due to arterial stenosis.

Murmurs

Murmurs, or ***bruits,*** are abnormal sounds heard in various parts of the vascular system. The two terms are used interchangeably, though *murmur* is more commonly used to denote noise heard over the heart than over blood vessels.

Blood flow is laminar and nonturbulent up to a critical velocity; above this velocity, and beyond an obstruction, blood flow is turbulent. Laminar flow is silent, but turbulent flow creates sounds. Blood flow speeds up when an artery or a heart valve is narrowed.

Examples of vascular sounds outside the heart are the *bruit* heard over a large, highly vascular goiter, the bruit heard over a carotid artery when its lumen is narrowed and distorted by atherosclerosis, and the murmurs heard over an aneurysmal dilation of one of the large arteries, an arteriovenous (A-V) fistula, or a patent ductus arteriosus.

The major, but certainly not the only, *cause of cardiac murmurs* is disease of the heart valves. When the orifice of a valve is narrowed (***stenosis***), blood flow through it in the normal direction is accelerated and turbulent. When a valve is incompetent, blood flows backward through it (***regurgitation*** or ***insufficiency***), again through a narrow orifice that accelerates flow.

The timing (systolic or diastolic) of a murmur due to stenosis or insufficiency of any particular valve (*Table*) can be predicted from a knowledge of the mechanical events of the cardiac cycle. Murmurs due to disease of a particular valve can generally be heard best when the stethoscope is over that particular valve; thus-

i. Murmurs due to disorders of the aortic and pulmnonic valves are usually heard best at the base of the heart
ii. Murmurs due to mitral disease are usually heard best at the apex.

Table. *Heart murmurs.*

Valve	*Abnormality*	*Timing of Murmur*
Aortic or pulmonary	Stenosis	Systolic
	Insufficiency	Diastolic
Mitral or tricuspid	Stenosis	Diastolic
	Insufficiency	Systolic

There are other aspects of the duration, character, accentuation, and transmission of the sound that help to locate its origin in one valve or the other. One of the loudest murmurs is that produced when blood flows backward in diastole through a hole in a cusp of the aortic valve. Most murmurs can be heard only with the aid of the stethoscope, but this high-pitched musical diastolic murmur is sometimes audible to the unaided ear several feet from the patient.

In patients with *congenital interventricular septal defects*, flow from the left to the right ventricle causes a *systolic murmur.*

Soft murmurs may also be heard in patients with interatrial septal defects, although they are not a constant finding.

Soft systolic murmurs are common in individuals, especially children, who have no cardiac disease.

Systolic murmurs are also common in anemic patients as a result of the low viscosity of the blood and the rapid flow.

(Ref. Ganong 22th edition; Page 569)

Auscultation

Process of listening for sounds within the body, usually the sounds of thoracic or abdominal viscera by stethoscope inorder to detect some abnormallity.

(Ref. Taber's)

Apparatus for auscultating heart sounds : Heart sound can be detected by :

i. Clinical stethoscope
ii. Haemo-cardiography,
iii. Microphone with oscillography, and also recorded by the phonocardiograph.

Apex beat

Definition : Apex beat is the lowest and outer most point of definite cardiac pulsation.

(Ref. Hutchison's)

Location :

In the left 5th intercostal space, 9 cm from the midsternal line just medial to the left nipple.

Importance :

1. Measurement of hear rate.
2. Position of heart- whether dextrocardia or not.
3. Different heart disease diagnosis
4. Displacement of mediastinum due to pneumothorax, pleural effusion, left ventricular hypertrophy etc.

Pulse

Definition : Pulse is the rhythmic dilatation and elongation of arterial wall as a result of pressure changes created by the intermitten ejection of blood from heart to the already full aorta feeding the arterial system, transmit as a wave to the periphery.

Normal pulse rate :

i. Range : 60-90 /minute
ii. Average : 72 /minute.

Normal pulse

(Description of a pulse) : Normal pulse tracing is called catacrotic pulse. Pulse has a upstroke and down stroke wave, The upstroke wave is ***P*** and have no secon-dary wave in it. It is also called percussion wave. Near the middle of the downstroke there is a sharp depression called dicrotic notch ***D*** which is followed by a small wave called dicrotic

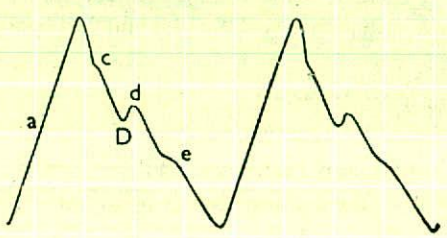


Fig. 6-5. *Normal pulse tracing.*

wave ***d***. Some time secondary oscillation may present above and below the dicrotic notch, These are called pre and post diorotic notch respectively.

P or percussion wave : It is the wave from the starting of the wave upto dicrotic notich, It coincides with ventricular systole.

Dicrotic notch : It is due to sharp fall of arterial pressure. At the end of the systole, aortic valve closes then the column of blood rolling towards left ventricle.

Dicrotic wave : It is due to refluxion of blood on the semilunar valve and produces this wave, It coincides with ventricular diastole.

Classification of pulse

On the basis of site :

A. *Arterial pulse :*
   i. Normal or catacrotic
   ii. Abnormal Pulse-
      a. Anacrotic pulse
      b. Dicrotic pulse
      c. Collapsing pulse
      d. Pulsus paradoxas
      e. Pulsus atterna's
      f. Pulsus bisferiense
      g. Pulsus deficit.

B. *Venous pulse.*

Arterial pulse depends upon :

i. Intermittent discharge of blood from the contracting left ventricles into the arterial system (aorta).
ii. Resistance to the blood in its passage from arterioles in to the capillaries.
iii. The elasticity of vessel wall.

Q. ***What are the points you will remember while examining a pulse ? or***
 # What do you understand by feeling a pulse?

Ans. During examining a pulse we remember the following points :

1. *Rate :* It is the number of pulse per minute. Normally it coincides with heart rate.
2. *Rhythm :* It indicates wheather the beats are equidistant or not that is either regular or irregularly regular or irregularly irregular.
3. *Volume :* It indicates the rise of pulse wave above the diastolic level. It varies with stroke volume. The greater the stroke volume the greater the volume of pulse.
4. *Condition of vessel wall :* By feeling the pulse we can know the condition of the blood vessels-
   a. Soft and easily compressable pulse indicates low cardiac output.
   b. Hard and not compressable pulse indicates atherosclerosis.
5. *Tension :* It is the approximate measure of systolic pressure.
6. *Character :* Wheather normal or abnormal.
7. Radio-femoral delay.

Site of feeling a pulse :

A. *Arterial pulse :*
   1. Radial artery
   2. Brachial artery
   3. Axillary artery
   4. Carotid artery
   5. Facial artery
   6. Femoral artery
   7. Popliteal
   8. Posterior tibial artery.
   9. Arteria dorsallis pedis.

B. *Venous pulse :* Jugular vein.

Procedure of feeling pulse :

Pulse are felt by placing three fingers side by side on the radial artery. Fingers are- index, middle and ring finger.

Q. ***What indicates three fingers?***

Ans.

a. *Index or proximal finger :* Adjust the pressure.
b. *Middle finger :* Remains stationary and feels the appearence and disapperarence of pulse wave.
c. *Ring or distal finger :* Applies a constant maximum pressure to stop retrograde ulnar colateral pulsation.

Significance of pulse :

1. *A Large primary wave indicates :*
   a. Large stroke volume
   b. Low peripheral resistance
   c. Slow heart rate.
2. *A small primary wave indicates :*
   a. Small output
   b. Rapid heart rate.
   c. High peripheral resistance
   d. Stiffness of vessel wall.

Abnormal pulses

1. *Anacrotic pulse :* When a secondary wave is found in the upstroke of pulse traching then it is called anacrotic pulse.
2. *Dicrotic pulse :* When the dicrotic wave become prominent and felt with finger then it is called dicrotic pulse.
3. *Sinus arrythmia :* When the frequency of pulse is

increased during inspiration and falls during expiration called sinus arrythmia. It is normally found in children but less commonly in adult, It occurs due to alternation of vagal tone during inspiration.

4. *Collapsing pulse (Water hammer pulse)* : It is characterised by rapid upstroke and decend of pulse wave without di crotic wave or notch. *Cause :* Aortic incompetence, patent ductus arteriosus, arteriovenous communication.
5. *Pulsus Bisferiens :* It is the combination of slow rising and collapsing pulse. *Cause :* Aortic stenosis and aortic regurgitation.
6. *Pulsus paradoxus :* Occationally the strength of pulse become strong, then weak, then strong, then weak and goes synchrony.
   Cause : pericardial effusion.
7. *Pulsus alternates :* The amplitude of pulse become alternately large and small. *Cause :* Hypertension, left vantricular forces (LVF).

(Ref. Guyton & Hall 11th edition and others)

Velocity of pulse wave

The speed at which the pulse wave travels. It is much more rapid (about 6 times) than the velocity of blood flow.

It depends on two factors :

i. Elasticity of vessel wall.
ii. Inertia of blood.

The velocity of pulse wave increases with age, as the co-efficient of elastic recoil diminishes.

Elasticity of vessel wall

The term is meant by the percentage increase in the volume of the artery with each mm of Hg rise in blood pressure.

Inter relation ship of velocity of pulse wave with elasticity and age-

Age	*Velocity*	*Elasticity*
5	3.6	0.47
20	5.2	0.33
40	7.1	0.24
70	9.5	0.18

Comment : With increasing age, velocity of pluse wave increases but elasticity of vessel wall decrease.

Jugular venous pulse (JVP)

'The internal jugular vein is in direct continuity with the right atrium. Observation of the column of blood in the internal jugular system is therefore a good measure of right atrial pressure.

Measurement : The jugular venous pressure is the vertical height between the manubriosternal angle and the top of the venous wave. The normal jugular venous pressure is usually 3-4 cm H_2O (the patient is positioned at about 45° to the horizontal while measuring JVP.

Jugular venous pulse wave : The jugular venous pressure wave is consists of the three peaks and two troughs. The peaks are described as a, c, and v waves and the troughs are known as x and y descents.

i. The a wave is produced by atrial systole
ii. The c wave is produced by early atrial relaxation
iii. The x descent occurs by atrial relaxation
iv. The v wave is produced by venous return fills the right atrium during continued ventricular systole
v. The y descent follows the v wave when the tricuspid value opens (fall in pressure).

Cardic Output

Definition : The amount of blood that ejected by each ventricle per minute is called cardiac output.

Or Cardiac out put is the quantity of blood pumped into the aorta each minute by the heart.

(Ref. Guyton & Hall-11th Edition; Page 232)

The Cardiac output can also be stated as a product of stroke volume and heart rate i.e.

CO = Stroke volume x heart rate
= 70 x 72 (*Here, Stroke volume = 70 ml/beat Heart rate = 72 beats/minute*)
= 5042 ml
= 5.04 liter/minute.
= About 5 liters/minute. *(Ref Ganong 22th edt page 570)*

Normal values of cardiac output :

i. For young, healthy men, resting cardiac output averages about : 5.6 liters/ minute.
ii. For woman, this volume is 10 to 20 percent less.
iii. The average cardiac output for the resting adult, is often stated to be almost exactly : 5 liters /minute.

(Ref. Guyton & Hall-11th Edition; Page 232)

Cardiac index

The cardiac output per minute per squire meter of body surface area is called cardiac index. *(3.2 L/min/Sq.m - Ganong)*

The average value is = 3.5 liter/min/sq.m of body surface area.

(Ref. Selkert 5th page -273)

Minute volume

It is the volume of blood ejected by each ventricle per minute. It

can be calculated by multiplying the rate of heart per minute by stroke volume.

Minute volume = Heart rate per minute x Stroke volume
= 76 x 70
= 5,250 ml.

Distribution of cardiac output

Cardiac output is distributed as follows :

Organs	*Cardiac output*		*% of total CO*
Liver	1450	ml/ minute	29 % of total CO
Kidney	1200	ml/ minute	21 % of total CO
Brain	750	ml/minute	15 % of total CO
Muscle	600-900	ml/minute	12-18 % of total CO
Coronary	225	ml/minute	4-5 % of total CO
Skin	400	ml/minute	8 % of total CO

(Ref. Guyton & Hall-11th edition)

Cordiac output & regional blood flow in a sedentary man

	Quite standing ml/min	*Exerise ml/min*
Cordiac outpur	*5900*	*24,000*
Blood flow to :		
Heart	*250*	*1000*
Brain	*750*	*750*
Active skeletul mucle	*650*	*20850*
Inactive skeletal muscle	*650*	*300*
Skin-	*500*	*500*
Kidney, liver, gastro intestinal tract etc.	*3100*	*60*

Factors affecting the cardiac output

The factors influence or affecting the cardiac output are :

A. *Physiological :*
1. *Age :* Cardiac output increases with age.
2. *Sex :* Cardiac output is 10% to 20% less in female than male due to less body wt. and surface area etc.
3. *Surface area :* More surface area more will be cardiac output.
4. *Posture :* Cardiac output is greater in sitting and lying than errect posture due to less venous return in errect posture
5. *Exercise :* Cardiac output markedly increases in severe exercise and small amount in moderate exercise due to excess muscular activity and venous return.
6. *Emotion :* Increases cardiac output.
7. *Temperature :* It increase heart rate thence cardiac output.

B. *Pathological :*
1. *Hyperthyroidism :* It increases CO due to increase heart rate and increase body metabolism.
2. *Anaemia :* In anaemia O_2 carrying capacity decreased to compensate this CO increases.
3. *Fever :* CO increases in fever due to increase metabolism and temperature.
4. Fibrilation & Flutter.
5. *Other condition :* Paget's disease, arterio-venous fistula.

Cardiac output decreases in :

a. Hypothyroidism
b. Haemorrhage
c. Congestive cardiac failure
d. Shock
e. Oligaemia.

Effect of various conditions on cardiac output

1. *No change :*
   a. Sleep
   b. Moderate changes in environmental temperature.
2. *Increase :*
   a. Anxiety and excitement (50-100%)
   b. Eating (30%)
   c. Exercise (up to 700%)
   d. High environmental temperature
   e. Pregnancy
   f. Epinephrine.
3. *Decrease :*
   a. Sitting or standing from lying position (20-30%)
   b. Rapid arrhythmias
   c. Heart disease.

(Ref Ganong 22th edition; page-572)

Factors Regulating Cardiac Output

1. *Venous return :* Any thing that increases or diminishes the venous return will alter the CO accordingly. Increased venous return increases end diastolic volume ' increases stroke volume, that increases CO.

   It depends on :
   a. Muscular activity.
   b. Pumping action of heart.
   c. Pressure gradient in vessels.
   d. Respiratory pump.

e. Gravity.

f. Vasomotor tone

2. *Force of contraction of heart :* When force of contraction of heart increases cardiac output also increases.

   It depends on :

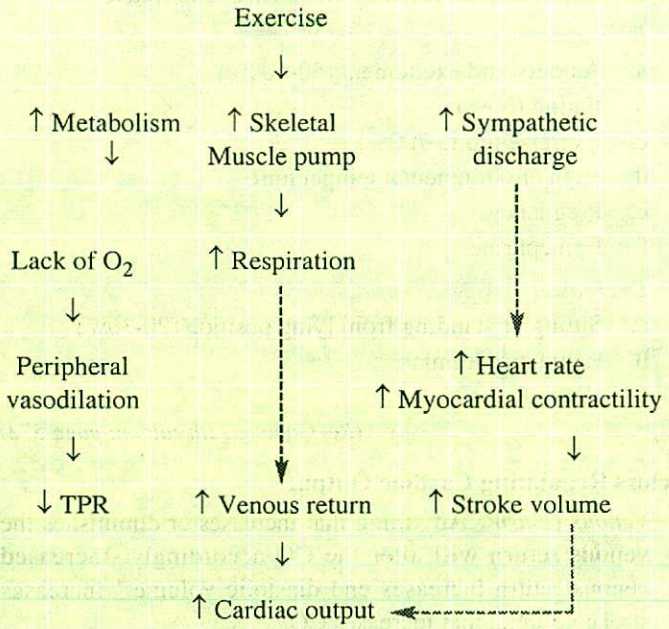
   a. Initial length of muscle fibre.
   b. Nutrition and O_2 supply of heart
   c. Diastolic phase.
   d. Sympathetic stimulation
   e. Circulating hormone level
   f. Ca^{++} level in blood.

3. *Frequency of heart beat :* Cardiac output is the product of stroke volume and heart rate. That is cardiac output = stroke vloume x heart rate. So, if stroke volume remains constant, then increased heart rate increases the cardiac out put that is cardiac out put is directly proportional to heart rate.

4. *Ejection fraction :* The fraction of end diastolic volume that is ejected is called the ejection fraction- usualy equal to about 60% of end diastolic volume.

5. *Peripheral resistance :* Increased peripheral registance → decreases venous return → decreased end diastolic volume → decreased stroke volume → decreased cardiac output.

Q. ***How Exercise increase cardiac output ?***



Methods of cardic output measurement

Cardiac output can be measured by the following way -

A. *Direct methods* (In animals).

B. *Indirect methods* (In human beings) : It is done by the help of following methods :

   a. Fick principle method by using O_2 or CO_2.
   b. Dye methods or indicator dilution technique
   c. Ballisto-cardiography.
   d. Heart lungs preparation.

Fick Principle Methhod

Fick principle : Fick principle states that the amount of a substance taken up by an organ (or by the whole body) per unit of time is equal to the arterial level of the substance minus the venous level (A-V difference) times the blood flow.

Consumption of a substance (ml/min) =

Arterio-venous difference (AO_2 - VO_2) of that substance
Blood flow (cardiac output).

This principle can be applied, of course, only in situations in which the arterial blood is the sole source of the substance taken up. The principle can be used to determine cardiac output by measuring the amount of O_2 consumed by the body in a given period and dividing this value by the A-V difference across the lungs. Because systemic arterial blood has the same O_2 content in all parts of the body, the arterial O_2 content can be measured in a sample obtained from any convenient artery.

A sample of venous blood in the pulmonary artery is obtained by means of a cardiac catheter. Right atrial blood has been used in the past, but mixing of this blood may be incomplete, so that the sample is not representative of the whole body. An example of the calculation of cardiac output using a typical set of values is as follows :

$$CO = \frac{O_2 \text{ consumption (ml/min)}}{\text{Arterio venous difference. } (AO_2 - VO_2)}$$

About 250 ml of O_2 are absorbed by the pulmonary blood from lungs per minute.

The arterial blood O_2 level is 190 ml/liter of blood and venous level of O_2 is 140 ml/liter of blood. So the arterio-venous difference is 50 ml/liter.

$$= \frac{250 \text{ ml/minute}}{\text{190 ml/L arterial blood - 140 ml/L venous blood in pulmonary artery.}}$$

$$= \frac{250 \text{ ml/minute}}{(190\text{-}140) \text{ ml /liter}}$$

$$= \frac{250}{50} \text{ liter/minute}$$

$$= 5 \text{ liter/minute.}$$

So , cardiac output is about 5,000 ml/minute or 5 liter/minute.

It has now become commonplace to insert a long catheter through a forearm vein and to guide its tip into the heart with the aid of a fluoroscope. Catheters can be inserted not only into

the right atrium but also through the atrium and the right ventricle into the small branches of the pulmonary artery.

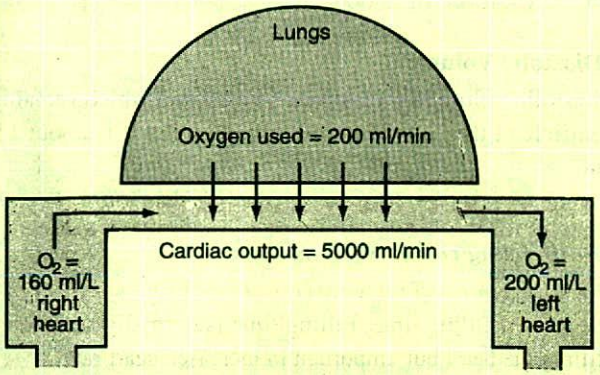


Figure. 6-6. *Fick principle for determining cardiac output.*

Catheters can also be inserted in peripheral arteries and guided in a retrograde direction to the heart and into coronary or other arteries.

(Ref. Ganong 22th Edition; Page 570)

Indicator dilution technique or dye method :

Principle : In measuring the cardiac output by the so-called indicator dilution mithod, a small amount of indicator, such as a dye, is injected into a large vein or, preferably, into the right atrium. This passes rapidly through the right side of the heart, the lungs, an the left side of the heart and, finally, into the arterial system. Then one records the concentration of the dye as it passes through one of the peripheral arteries, giving a *curve* such as one of the two curves shown in figure.

Procedure : In each of these instances, 5 milligrams of Cardio-Green dye was injected at zero time. In the top recording, none of the dye passed into the arterial tree until about 3 seconds after the injection, but then the arterial concentration of the dye rose rapidly to a maximum in about 6 to 7 seconds. After that, the concentration fell rapidly. Before the concentration reached the zero point, some of the dye had already circulated all the way through some of the peripheral vessels and returned through the heart for a second time. Consequently, the dye concentration in the artery began to rise again. For the purpose of calculation, it is necessary to extrapolate the early down-slope of the curve to the zero point, as shown by the dashed portion of the curve. In this way, the extrapolated time-concentration curve of the dye in an artery, without recirculation, can be measured in its first portion and estimated reasonably accurately in its latter portion.

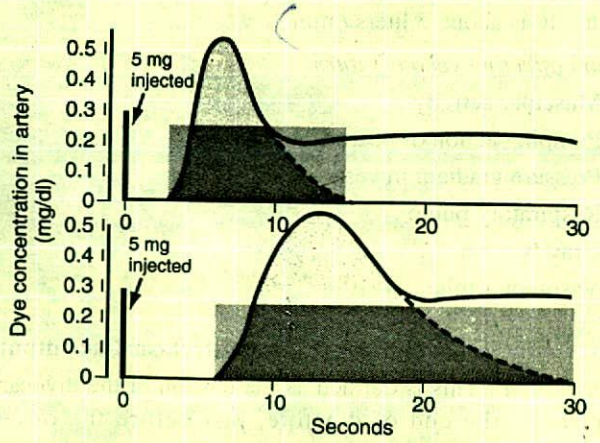


Figure. 6-7. *Extrapolated dye concentration curves used to calculate two separate cardiac output levels by the dilution method. (The rectangular areas are the calculated average concentrations of dye in the arterial blood for the durations of the respective extrapolated curves.)*

Once the extrapolated time-concentration curve has been determined, one can then calculate the mean concentration of dye in the arterial blood for the duration of the curve. In the top example of *figure*, this was done by measuring the area under the entire extrapolated curve and then averaging the concentration of dye for the duration of the curve; one can see from the shaded rectangle straddling the upper curve of the figure that the average concentration of dye was about 0.25 mg/dl of blood and that the duration of this average value was 12 seconds. A total of 5 milligrams of dye was injected at the beginning of the experiment. For blood carrying only 0.25 milligram of dye in each deciliter to carry the entire 5 milligrams of dye through the heart and lungs in 12 seconds, a total of 20 1-deciliter portions of blood would need to pass through the heart during this 12 seconds time, which would be the same as a cardiac output of 2 L/12 second or 10 L/minute.

To summarize, the cardiac output can be determined using the following formula :

$$\text{Cardiac output (ml/minute)} = \frac{\text{Milligrams of dye injected} \times 60}{\text{Average concentration of dye in each milliliter of blood for the duration of the curve} \times \textit{Duration of the curve in seconds}}$$

(Ref. Guyton& Hall-11th edition; Page 244)

Q. ***What are the purpose of cardiac output measurement?***

1. For investigation of congenitial & acute heart disease.
2. For investigation of cardiac septal defect.

Stroke volume

Definition : The amount of blood pumped out by each ventricle in each beat is called stroke volume . It is about 70 ml.

Stroke volume = (End diastolic volume - End systolic volume)

(Ref. Guyton & Hall-11th Edition, Page-108)

Stroke volume index

Stroke volume per square meter of body surface area is called

stroke volume index. It is about 47 ml.

$$= \frac{\text{Stroke volume}}{\text{Surface area}}$$

$$= \frac{80}{1.7}$$

= 47 ml.

Relation between cardiac output, stroke volume and heart rate

Cardiac output = Stroke volume x heart rate.

So, when cardiac out put remain constant, stroke volume and heart rate bears an inverse proportional to each other. That is -

i. Increase heart rate, decreases stroke volume.
ii. Increases stroke volume, decreases heart rate.

Factors affecting stroke volume :

1. Venous return : Stroke volume $\propto$ Venous return.
2. Heart rate ; SV $\frac{1}{\propto}$ Heart rate.
3. Force of contraction : SV $\propto$ Force of contraction.
4. Total peripheral resistance : SV $\frac{1}{\propto}$ TPR

End systolic volume

The end systolic volume is that volume of blood which remains in each ventricle at the end of the ventricular systole. It is about 40-50 ml.

(Ref. Guyton & Hall-11th Edition, Page-108)

Factors affecting end systolic volume :

a. *Pressure load :* It is the pressure within the aorta . If the aortic pressure is within physiological limit the heart can eject all blood . But if the aortic pressure is not within physiological limit, unless the tension of myocardium is increased, the heart can not eject all blood.

b. *Myocardial contractility :* Heart responds the excitation by contraction. This phenomenon occurs due to chemical and mechanical changes in the contractile elements - actin and myosin.

Normally, heart muscle remain relaxed. Actin, myosin remains dissociated and Ca^{++} is in the sarcoplasmic reticulum When an impulse reaches myofibriles, the Ca^{++} stimulated and the enzyme ATPase which break down the ATP to release energy that helps formation of actin-myosin complex, which causes gliding of actin and myosin . The agent, which increases the contractility is called ionotropic.

The force of contraction of heart depends upon :

i. Initial length of muscle fibres
ii. Nutrition and O_2 supply
iii. Sympathetic stimulation.
iv. Diastolic period.
v. Homometric and heterometric autoregulation
vi. Circulating hormone.
vii. Ca^{++} level of blood.

End Diastolic Volume

End diastolic volume is that volume of blood which remains in the ventricle at the end of ventricular diastole. It is about 110 - 120 ml.

(Ref. Guyton & Hall-11th Edition, Page-108)

Factors affecting end diastolic volume :

a. *Filling time :* The ventricular filling is affected by decreased filling time. Filling time is normally adequate for filling the heart but important in increased heart rate .

b. *Effective filling pressure :* This is the gradient between the inside and out side of the ventricle. It depends upon-
   i. Degree of positivity of intra abdominal pressure.
   ii. Degree of negativity of intrathoracic pressure.

c. *Distensibility of the ventricle :* Heart muscle is distended during diastole to receive blood from periphery. It depends on :
   i. Condition of pericardium.
   ii. Condition of myocardium.

d. *Atrial contraction :* It contributes 30% of blood, when atria contract, and pushed the blood into the ventricle. It is important during increased heart rate .

e. *Venous return :* Increased venous return increases the ventricular filling that increases end diastolic volume.

f. *Ejection fraction :* The fraction of end diastolic volume that is ejected is called the ejection fraction.

Venous return

Definition : It is the amount of blood that come from periphery to right atria of heart in each minute. It is equal to cardiac output . It is about 5 liters / min.

Factors affecting venous return

i. Muscular activity .
ii. Pumping action of heart .
iii. Pressure gradient in vessels.
iv. Respiratory pump .
v. Gravity .
vi. Vasomotor tone .

Q. 06. **Define preload. How preload affect cardiac output?**

i. *Definition* : This is defined as the tension of the myocardial fibres at the end of diastole, just before the onset of ventricular contraction. Preload is therefore related to the degree of stretch of the myocardial fibres.

ii. *Factors affecting pre-load* : In the intact heart the preload

depends on :

a. Ventricular end-diastolic volume
b. Venous return
c. Venous tone
d. Body position
e. Intrathoracic and intrapericardial pressure
f. Atrial contraction.

iii. *Preload affect cardiac output* : Pre-load is one of the major factors that control the force of contraction. An increase in pre-load improves myocardial oxygen consumption and thus increases myocardial force of contraction and so stroke volume and cardiac output.

Q. 07. **Define afterload. How afterload affect cardiac output.**

i. *Definition* : This is the load or resistance against which the ventricle contracts (or this is defined as the myocardial wall tension developed during systolic ejection).

ii. *It is formed by* :

a. Pulmonary and systemic resistance
b. Physical characteristics of the vessel walls
c. Volume of blood that is ejected.

iii. Right ventricular afterload is normally negligible because the resistance of the pulmonary circulation is very low.

iv. *Determinants of afterload* : In the case of the left ventricle the determinants of afterload are :

1. Resistance imposed by the aortic value
2. Peripheral vascular resistance
3. Elasticity of the major blood vessels.

Mean systemic filling pressure

It is the average effective pressure of blood in peripheral circulation, which tends to push the blood to the right atrium.

MSF pressure = 7mm of Hg.

Factors affecting mean systemic filling pressure

A. *Factors increasing mean systemic filling pressure :*

a. Increased blood volume causes increase *mean systemic filling pressure :*
   i. Acute increase15% *Double increase*
   ii. Chronic increase 30% *MSF pressure*
b. Maximum sympathetic innervation.
c. Skeletal muscle contraction.

B. *Factors decreasing mean systemic filling pressure :*

a. Absence of sympathetic innervation.
b. Decrease blood volume.

C. *Homometric autoregulation* : Homo means no change and metric means length. It is a process in which power is added to the cardiac output of the heart to eject the optimum amount of blood without change in the length of muscle fibres, hormonal or nervous influence.

D. *Heterometric autoregulation* : Hetero means change and metric means length. Heart muscle can eject optimum amount of blood without hormonal or nervous influence, but by simple increasing the length and thereby increasing its force of contraction.

E. *Vasomotor tone* : Under normal condition the vasoconstriction area of the vasomotor center transmit signals continually to the sympathetic vasoconstrictor nerve fibers, causing continuous slow fireing of these fibre.This continuous slow fireing is called sympathetic vasoconstrictor tones. This impulse maintain a partial state of contraction in the blood vessels is called vasomotor tone.

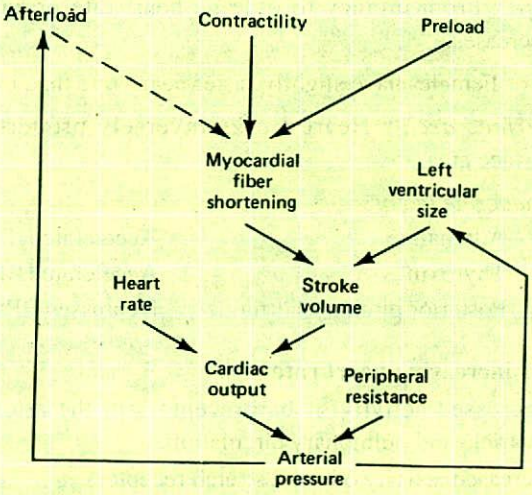
Peripheral resistance

It is the resistance in which blood has to over come while passing through the periphery.

Factors affecting peripheral resistance : Factors on which the peripheral resistance depends-

i. Velocity of blood
ii. Viscosity of blood
iii. Elasticity of arterial walls
iv. State of lumen of blood vessels.

Table. **Interactions between the components that regulate cardiac output and arterial pressure. Solid lines indicate increases and the dashed line indicates a decrease.**



Heart rate

Definition : The number of heart beat per minute is called heart rate.

Normal heart rate :

1. Adult (Range) : 60-90 /minute

	Average	: 72	/minute
2.	In foetus	: 140-150	/minute
3.	In Newborn	: 130-140	/minute
4.	In children	: 80-120	/minute
5.	In old age	: 75-80	/minute

Factors affecting heart rate

1. *Higher Centre :* Stimulation of posterior group of hypothalamic nucleus increases heart rate, while middle group decreases heart rate, stimulation of area 13 of frontal lobe, causes tachycardia.
2. *Respiration :* Heart rate increases during inspiration particularly in children and decreases during expiration.
3. *Cardio-vascular reflexes :*
   a. Baro-receptor reflex -Stimulation of baro receptor decreases the heart rate.
   b. Bain - Bridge reflex - Stimulation of bain Bridge increases heart rate.
4. *Temperature :* Increase body temparature, increases heart rate by directly stimulating the SA node.
5. *Intra cranial pressure :* Increase intracranial pressure stimulates cardio-inhibitory centre and causes slowing heart rate.
6. *Muscular exercise :* It increases heart rate by -
   i. Decreasing O_2, increasing CO_2 & H^+ tension.
   ii. Increasing body temparature.
   iii. Increasing venous return.
   iv. Increasing secretion of adrenalin.
7. *Age :* From infancy to old age heart rate progressively decreases.
8. *Sex :* Females have slightly faster heart rate than male.
9. *Surface area :* Heart rate is inversely proportional to surface area.
10. *Endocrine factors :*
    a. Adrenaline : Accelerate HR.
    b. Thyroxin : Accelerate HR.
    c. Posterior pituitary hormone : Depresses HR.

Factors increasing heart rate

1. Decreased activity of baroreceptors in the arteries, left ventricle and pulmonary circulation.
2. Increased activity of atrial stretch receptors
3. Inspiration
4. Excitement.
5. Anger
6. Most pain stimuli.
7. Hypoxia
8. Exercise.
9. Fever.
10. Epinephrine and norepineprine.
11. Thyroid hormone.
12. Bainbridge reflex.

(Ref Ganong 22th edition; Page 610)

Factors decreasing heart rate

1. Increased activity of baroreceptors in the arteies, left ventricle and pulmonary circulation.
2. Expiration.
3. Fear
4. Grife
5. Increased intra cranial pressure
6. Stimulation of pain fibres in trigeminal nerve.
7. Athlets .

(Ref Ganong 22th edition; Page 610)

Q. 00. **What is sinus arrhythmia**?

Ans. Cardiac irregularity characterised by an increa- sed heart rate during inspiration and decrease in heart rate on expiration. This arrythmia has no clinical significance except in older patients, in whom it may occur in coronary artery diseases.

(Ref. Tabers)

Cause : It may result from any one of many circulatory reflexes that altered the sympathetic and parasympathetic nerve signals to the heart sinus node.

(Ref. Guyton & Hall-10th Edition; Page 148)

Tachycardia

The trem trachycardia means fast heart rate. Increased heart rate above the upper normal physiological limit, usually above 100 beats/ min, is called tachycardia.

(Ref. Guyton & Hall-10th Edition; Page 147)

Cause of tachycardia :

i. *Increased body temperature* : The rate of the heart increases about 10 beats per minute for each degree Fahrenheit (18 beats per degree Celsius) increase in body temperature upto a body temperature of 105°F (40°C); beyond this, the heart rate may decrease because of progressive weakening of the heart muscle as a result of fever.

   Fever causes tachycardia because increased temperature increases the rate of metabolism of the sinus node, which in turn directly increases its excitability and rate of rhythm.

ii. Stimulation of heart by sympathetic nerve : Many factors may caues the sympathetic nervous system to excite the herat. For instant, when a patient loses blood and passes into a state of shock or semishock, sympathetic reflex stimulation of the heart can increase the heart rate to 150 to 180 beats per minute.

iii. Toxic conditions of the heart : Simple weakening of the myocardium usually increases the heart rate because the

weakened heart does not pump blood into the arterial tree to a normal extent, and this elicits sympathetic reflexes to increase the heart rate.

(Ref. Guyton & Hall-10th Edition; Page 147)

Q. 00. **What is sinus tachycardia?**

Ans. A sinus rate of more than 100/minute is called sinus tachycardia.

Causes of sinus tachycardia are :

i. *Physiological* :
   a. An increase in sympathetic activity associated with exercise, emotion.
   b. Pregnancy

ii. *Pathological* :
   a. Anxiety
   b. Fever
   c. Anaemia
   d. Heart failure
   e. Thyrotoxicosis
   f. Phaeochromocytoma
   g. Drugs, e.g. beta-adrenoceptor agonists (bronchodilators)

Bradycardia

The term bradycardia means a slow heart rate. Decreased heart rate below the lower normal physiological limit, usually below 60 beats/ min, is called bradycardia.

(Ref. Guyton & Hall-10th Edition; Page 147)

Cause of bradycardia :

i. Athletes : The athlete's heart is considerably stronger than that of a normal person, a fact that allows the athlete's heart to pump a large stroke volume output per beat even during periods of rest. The excessive quantities of blood pumped into the arterial tree with each beat initiate feedback circulatory reflexes or other effects to cause bradycardia when the athlete's is at rest.

ii. Vagal stimulation : Any circulatory reflex that stimulates the vagus nerve can cause the heart rate to decrease considerably i.e carotid sinus syndrome.

iii. Shock.

(Ref. Guyton & Hall-10th Edition; Page 147, 148)

Q. 00. **What is sinus bradycardia?**

Ans. A sinus rate of less than 60/minute is called sinus bradycardia.

Causes of sinus bradycardia are :

i. *Physiological* :
   a. In normal people during sleep
   b. In athletes.

ii. *Pathological* :
   a. Myocardial infarction
   b. Sinus node disease (sick sinus syndrome)
   c. Hypothermia
   d. Cholestatic jaundice
   e. Raised intracranial pressure
   f. Drugs, e.g. beta-adrenoceptor antagonist, digoxin, verapamil.

Q. 00. **What is the relationship between heart rate and respiration?**

Ans. Heart rate increases during inspiration particu- larly in children and decreases during expiration.

Electrocardiogram (ECG)

Lead

Definition : It denotes the connection of galvanometer with wires to electrods. It is used to traching of ECG.

Types :

It is mainly two types -

1. Bipolar or standard limb leads.
2. Unipolar limb leads.

In addition to these, there is another lead called chest lead.

Bipolar lead

It has two electrodes - One negative another positive. several standard locations are selected, so they are called standard limb leads.

The commonly used bi-polar leads are :

Lead	*Negative terminal*	*Positive terminal*
Lead - I	Right arm	Left arm
Lead - II	Right arm	Left leg
Lead - III	Left arm	Left leg

Lead-I : It records the difference of potentials between the right and left arm electrodes.

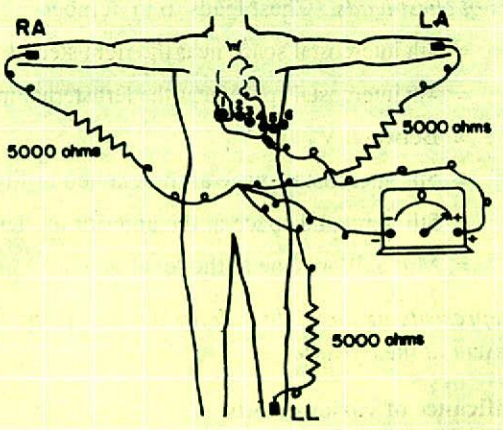


Fig. 6-9. *Leads.*

Lead-II : It records the difference of potentials between the right arm and left leg electrodes

Lead-III : It records the difference of potentials between the left arm and left leg electrodes.

Advantage of Bipolar lead :

i. They are advantageous in demonstrating disturbances of rhythm of heart.
ii. They also suggest genaralised lesions of heart like cardiomyopathies.

Disadvantage of Bipolar lead :

i. As they record the difference of potentials between the two electrodes it is difficult to denote a particular change in relation to single electrode.
ii. It is equally impossible to localize a change in potential in relation to site of lesion restricted to a specific region of the heart.

Unipolar lead

Though called unipolar it actually consists of two connecting leads-

a. *Exploring electrode :* One single electrode is placed at a selected position over the surface of the body.
b. *Indifferent or reference electrode :* Formed by the central terminal consisting of junctions of three different electrodes, placed at right arm, left arm and left leg.

The different unipolar lead are :

Lead	*Exploring electrode*
Lead - aVR	Right arm
Lead - aVL	Left arm
Lead - aVF	Left leg

Chest lead

Defferent point of the chest opposite the heart it gives the actual electrical changes or potential excitability of the heart.

Types of chest leads : Chest leads 6 in number-

V_1 = 4th intercostal space near the right sternal margin,
V_2 = 4th intercostal space near the left sternal margin.
V_3 = Between V_2 and V_4
V_4 = 5th intercostal space at midclavicular line.
V_5 = 5th itercostal space at the anterior axillary line.
V_6 = Mid axillary line at the level of V_4.

All represents at the right side of the heart but the V_5 and V_6 represent at the left side.

Significance of various leads

A. *Bipolar or standard limb lead :* Valuable for diagnosis of-
   i. Arrhythmia
   ii. Preliminary studies of the functional abnormalities of the heart.
B. *Unipolar limb leads :* Most valuable for-
   i. Determining the position of heart.
   ii. Confirming the significance of Q and T waves in the standard limbs.
   iii. Confirming the evidence of ventricular damage or hypertrophy.
C. *Chest leads :* Important for diagnosis or for-
   i. Localization of the recent or old ventricular damage.
   ii. Bundle branch block.
   iii. Detection of ventricular hypertrophy.

Einthoven's Law

Einthoven's law states that if the electrical potentials of any two of the three standard electrographic leads are known at any given instant. There one can be determined mathmati-cally from the first two by simply summing the first two. i. e. the sum total voltage in leads 1. and iii equals to the voltage in lead ii.

Einthoven's Triangle

It is an equilateral triangle drown arbitrarily around the area of the heart . The two apices at the upper part of the tringle

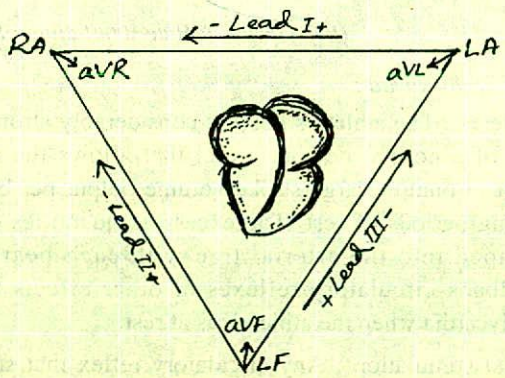


Fig.6-10. Einthoven's Triangle for recording the ECG form limb leads.

represents the points at which the two arm connects electrically with fluid around the heart and lower apex is that of the left leg.

Electrocardiogram (ECG)

Electrocardiogram is the recording from the surface of the body of the electrical changes of the heart in each cardiac cycle.

Description of a normal ECG : A normal ECG shows five consecutive waves PQRST. Of these there are three Positive waves; P, R & T and two negative waves, Q &S and a complex QRS.

1. ***P Wave*** : It is the first upward deflection. It is small, constant wave having a rounded or pointed top.

It represents atrial depolarization.

Duration : 0.10 second (< 0.125)

Voltage : 25 mv.

It indicates :

i. The impulse is originating at the SA node.
ii. It spreads over the atria in the usual direction
iii. There is no defect in conduction.
iv. The strength of contraction, the mass of atrial musculature and its nutrition are normal.

2. ***Q Wave*** : It is the downward deflexion. It is small & often inconspicuous.
   1. It represents septal depolarization.
   2. It is caused by the septal activity.
   3. Prominent Q wave indicates old infarction.

3. ***R Wave*** : It is upward deflection; most constant and conspicuous wave having the tallest amplitude
   It follows immediately upon Q wave.
   It represents apical left ventricular depolarization.

4. ***S Wave*** : It is the downward deflection just next to R wave.
   It represents posterior basal left ventricular depolarization.

5. ***T Wave*** : It is the repolarization wave of ventricles

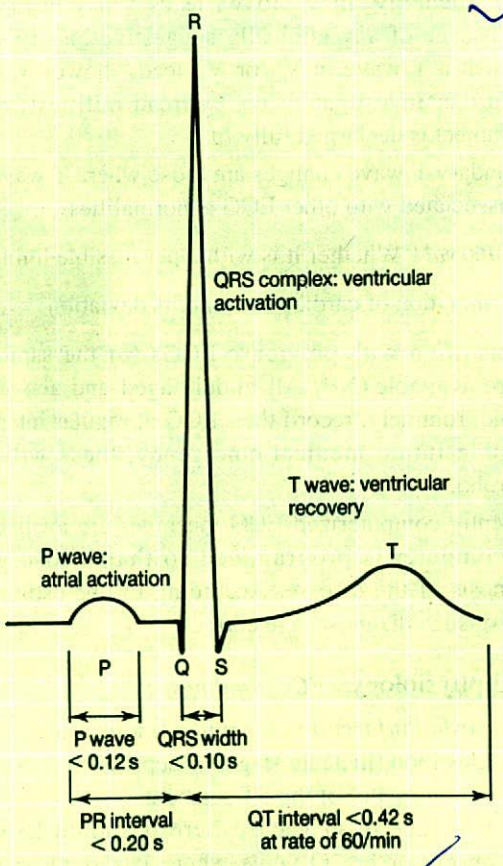


Fig. 6-11. *Tracing of the normal ECG.*

showing upward deflection. It represents ventricular repolarization.

Duration : 0.13second

Voltage : 0.2 to 0.4 mv.

6. ***ECG Complexes*** :
   1. *QRS complex :* It is the ventricular depolarization and atrial repolarization.
      Duration : 0.08-0.10 second.
   2. *QRST(QT) complex :* These four waves are caused by ventricular activity, are collectively known as ventricular complex i.e ventricular depolarization & ventricular repolarization.
      Duration : 0.40-0.43 second.

(Ref. Ganong 22th Edition; Page-551)

7. ***ECG intervals*** :
   i. ***P-R interval*** : It is the time or interval between the peak of P and R wave or between the start of P & Q wave.It is the atrial depolarization and conduction through AV node.
      Duration : 0.18 second (Range : 0.12-0.20 second).
      Importance :
      a. Increased P-R interval indicates that the conduction time from atria to ventricle is increased.
      b. 0.4 Sec P-R interval indicates that the complete heart block may occur at any time.

   ii. ***R-R interval*** : It is the interval between two successive R waves.
      Importance : Same R-R interval in next successive stages indicate rhythmic ventricular depolarization.

   iii. ***P-P interval :*** It is the interval between two successive P waves.
      Importance : Equal intervals in next succes-sive stages indicates rhythmical depolarization of the atrium.

   iv. ***T-P interval :*** Alteration of this interval indicates alteration of heart rate.

   v. ***ST interval*** : QT minus QRS i.e. ventricular repolarization. *Duration* : 0.32 second.

(Ref. Ganong 22th Edition; Page-551)

Importance of ECG

A. *Physiological :*
   i. Normal heart rate is counted
   ii. Condition of heart can be detected.

B. *Clinical :*
   i. Atrial and ventricular hypertrophy.
   ii. Myocardial infarction.

iii. Pericarditis.
iv. Systemic disease that effect the heart.
v. Arrythmia, fibrillation, flutter, abnormal pulse
vi. Effects of drugs -
   a. Digitalis
   b. Quinine.

Some important tips about ECG

1. In the bipolar leads, lead II is maximally +ve, R is tallest in lead II ; also in lead II, Q is absent and T is upright.
2. In the unipolar limb lead, aVR is mostly -ve. Here P and T are inverted, R is very small.
3. In the unipolar chest leads the R wave gradually becomes taller and taller from V_1 to V_5 and S becomes smaller and smaller from V_1 to V_5. Q is present in V_5 and V_6 but absent in V_1.
4. In all leads P wave, PR intervals, QRS complex have normal values and ST segment is isoelectric.

How to read ECG

Finally, some tips are given below, about how to read ECG records of a given subject :

1. ***Heart rate :*** The heart rate is counted as follows : Locate the peaks of any two successive R waves ; count the number of small divisions in between them (for example, say 20 small divisions). [This interval, from R to R peaks represents one cardiac cycle and in this example, has taken 20 small divisions or 0.4 sec]. The heart rate is 1500 divided by the number of divisions between the R to R peaks ; for example, in the example cited above, the heart rate is 1500 divided 20 = 75/min. The figure 1500 is obtained as follows : each small division = 0.04 sec. Therefore in 60 seconds there are 60 divided 0.04 = 1500 such divisions. In short, 1500 small divisions represent one minute.
2. ***Rhythm :*** See whether the rhythm is sinus or not. Sinus rhythm means where the pace maker is SAN. In sinus rhythm, the normal sequence of P,Q,R,S,T are maintained and p waves are upright where they should be upright.

   In a normal ECG record, the heart rate (HR) fluctuates. For example at the beginning of a given ECG record the HR may be 70/ min, but within a few seconds, as the ECG recording continues, the HR may be 75/min. This is normal and is due to (usually) respiration and is called normal sinus arrhythmia. The report, in this case should read, heart rate, varying between 70 to 75/min, sinus arrhythmia.
3. ***P wave :*** Look for, i. whether there is any evidence of atrial hypertrophy (big p wave), inversion of p wave where it should normally be upright (nodal rhythm), absence of p wave and so on.
4. ***QRS complex :***
   i. Look for Q wave abnormality. That is, whether Q is present where it should not be present, or Q is unusually big and so on.
   ii. Look for duration of QRS complex (ie, whether it is within 0.8 sec or at best within 0.1 sec), whether its shape is altered (eg. in left bundle branch block).
   iii. Whether RSR pattern is present.
   iv. Tallness of R wave and depth of S wave - whether they exceed permissible limit.
   v. Whether R becomes progressively taller from V_1 onwards, and so on.
5. ***ST Sgment :*** Whether it is on isoelectric line or elevated or depressed.
6. ***T Wave :*** The interpretation of T wave abnormality is most difficult. T wave may be inverted in leads where it should normally be upright, but that dose not automatically mean there is abnormality . Inversion of T wave where there is no other abnormality in ECG, called , primary T wave changes can be of 2 kinds :
   i. Where the inverted T wave is symmetrical and its apex pointed ; this is pathological and may mean myocardial infarction.
   ii. Where the inverted T wave has round apex, this (particularly in V_1 to V_3 leads) may be, specially in absence of any clinically suggestive history, harmless, such a T wave in V_4 or V_5 leads, however, should be further investigated (e.g.by tread mill test) before the subject is declarned fully fit.

   Secondary T wave changes are those where T wave changes are associated with other ECG abnormalities.
7. ***PR interval :*** Whether it is within permissible limit.
8. Determination of cardiac axis and its deviation.
9. Comparition with previouse ECGs (of the same subject) where available.(NB. All middle aged and above persons, should, routinely, record their ECG at regular intervals. In a possible future medical emergency, these will serve as controls).

   Currently computerized ECG machines are available where the computer is programmed so that is also gives the diagnosis of the disease. According to one estimate, about 85% of such diagnoses are correct.

Applied physiology *(ECG Findings) :*

1. ***Myocardial infarction :*** Common findings are-
   i. Elevation (in acute stage) or depression (in subacute or chronic state) of the ST segment.
   ii. Presence of Q wave where it should be normally absent or big Q wave where it should be normally present.

iii. Inversion of T wave.

iv. Normally the height of R wave progresses from V_1 to V_5 but in myocardial infarction this progressive increase in height does not occur.

2. ***Myocardial ischemia :*** Common finding is depression of ST segment which may or may not be associated with other signs. Presence of a normal ECG, however, does not rule out cardiac ischemia.

3. ***Hypertrophy :*** Left ventricular hypertrophy is usually associated with larger R in V_5 and V_6, deeper S in V_1, V_2 and left axis deviation. These changes may or may not be associated with inversion of T wave and depression of ST.

4. ***Heart Block :*** In AV block the PR interval is more than 0.2 sec. In bundle branch block the duration of QRS is more than 0.11 see. Presence of RSR (in V_1) pattern denotes right bundle branch block. Whereas a slurred and broad QRS in V_5 and V_6 denote left bundle branch block.

5. ***Hyperkalemia :*** In erarly stages of *hyperkalemia*, T wave becomes taller. As the hyperkalemia progresses, AV block and atrial paralysis develop, so that prolonged PR interval and absence of P are found in ECG record. QRS becomes prolonged due to delayed conductivity in the ventricular conducting system.

Q. 05. **What ECG changes you expected to find in hyperkalaemia.**

Ans. Common ECG findings in hyperkalaemia are :

i. *In erarly stages of hyperkalemia* : T wave becomes taller.

ii. *As the hyperkalemia progresses* AV block and atrial paralysis develop, so that-

a. Prolonged PR interval and absence of P are found in ECG record.

b. QRS complexbecomes prolonged due to delayed conductivity in the ventricular conducting system.

Q. 06. **What ECG changes you expected to find in myocardial infraction.**

Ans. Common ECG findings in myocardial infraction are :

i. Elevation (in acute stage) or depression (in subacute or chronic state) of the ST segment.

ii. Presence of Q wave where it should be normally absent or big Q wave where it should be normally present.

iii. Inversion of T wave.

iv. Normally the height of R wave progresses from V_1 to V_5 but in myocardial infarction this progre ssive increase in height does not occur.

Q. 07. **What ECG changes you expected to find in hypokalaemia.**

Ans. Common ECG findings in hypokalaemia are-

i. Flattening of T wave.

ii. Prolongation of QT interval

iii. Appearance of U wave on the end of the T wave.

Q. 07. **ECG changes in hypocalcaemia and hypercalcaemia.**

Ans.

i. In *hypocalcaemia* : Common ECG findings in hypocalcaemia is prolongation of the QT interval.

ii. In *hypercalcaemia* : Common ECG findings in hypercalcaemia is shortening of the QT interval.

Heart block

Q. 01. ***What is heart block? Classify heart block.**

I. *Definition :* Occationally transmission of the impulse throgh the heart is blocked at a critical point in the conduetive system is called heart block.

Sites of heart block : Most common points of heart block are

i. Between the atria and ventricle.

ii. One of the bundle branches of purkinje system

iii. Rarely between the SA node and the atrial musculature.

(Ref. Guyton 10th edition)

II. *Classification or types of heart block :* There are three types of heart block-

i. Sino-atrial heart block.

ii. Atrio-ventricular (A-V) heart block :

Degrees of A-V heart block :

a. *First degree heart block* : All the atrial impulses reaches the ventricle but the P-R interval is abnormally long.

b. *2nd degree heart block* : Not all atrial impulses are conducted to ventricles. There may be for exapmle, a ventricular beat following every second or every third atrial beat (2 :1 block, 3 : 1 block)

c. *3rd degree block or complete heart block* : When no impulse passes from atria to ventricle. It causes the *droped beat*. Here the atrial rate is faster than the ventricle, for this reason, ventricle escape from the control of atria.

(Ref. Ganong 22th edition)

iii. Bundle branch block and hemiblock.

*(Q. **Short notes on- Heart block. Ans. Pl follow the above).*

Q. 01. **Describe A-V type of heart block.**

i. *Definition :* When conduction of impulse between atria and ventricle is blocked.

ii. *Cause :*

a. Localized damage or depression of AV node.

b. Excessive stimulation of vagus nerve.

c. Localized destruction of AV bundle as a result of coronary infract.

d. Pressure on the AV bundle by arteriosclerotic paques.

e. Depression caused by various drug.

(Ref. Guyton 11th edition)

+ *Degrees of A-V heart block* : Pl follow the above. + ECG changes - From below)

Degrees of AV heart block :

1. *First degree heart block :* All the atrial impulses reaches the ventricle but the P-R interval is abnormally long.
2. *2nd degree heart block :* Not all atrial impulses are conducted to ventricles. There may be, for exapmle, a ventricular beat following every second or every third atrial beat (2 :1 block, 3 : 1 block)
3. *3rd degree block or complete heart block :* When no impulse passes from atria to ventricle. It causes the "droped beat". Here the atrial rate is faster than the ventricle, for this reason, ventricle escape from the control of atria.

(Ref. Ganong 22th edition)

Q. 01. **What changes take place in ECG in heart block..**

I. ***In AV block*** : The PR interval is more than 0.2 second.

Degrees of A-V heart block :

i. *First degree heart block* : AV conduction is delayed.
   a. One P wave per QRS complex
   b. P-R interval more than 0.22 second.

ii. *2nd degree heart block* : Some P wave conducts and other fails to go to the ventricles.
   a. Mobitz I block :
      * Progressive lengthening of PR interval
      * One non-conducted beat (P wave fails to conduct)
      * The PR interval before the blocked P wave is much longer than the PR interval after the blocked P wave.
   b. Mobitz II block :
      * PR interval of the conducted beats is constant
      * P wave is not followed by QRS complex.
   c. 2:1, 3:1 block :
      * 2 or 3 P waves per QRS complex
      * Normal and constant PR interval in the conducted beats.

iii. *3rd degree block or complete heart block* : No P wave conducts to the ventricle.
   * Variable P wave rate and QRS complexs
   * Abnormally shaped QRS complexes.

Q.Write short notes on-Third degree heart block)

II. ***In bundle branch block*** : The duration of QRS is more than 0.11 second.

a. Presence of RSR (in V_1) pattern denotes right bundle branch block.

b. Whereas a slurred and broad QRS in V_5 and V_6 denote left bundle branch block.

Bundle of His block

Here the conduction of impulse from AV node to Bundle of His is impaired. It may be right or left bundle block.

SA Heart block

Here SA node fails to generate or fail to transmit the impulse from SA node to the atrial muscle.

Cause :

i. Over vagal stimulation
ii. Vasovagal syndrom.
iii. Over dose of digitalis.

Cardiac Arest

Definition : It is a condition in which the rhythmic contraction of heart occationally stop due to greatly disturbed cardiac metabolism.

Causes :

1. Hypoxia of heart during anesthsia or when the coronary blood flow to the SA node is blocked.
2. Severe myocardial diseases.

Flutter

Flutter means extremely rapid heart beat with reasonably coordinated cotraction of cardiac muscle. The rate of flutter is usually 200-250 times per minute. The flutter occurs frequently in the atria and rarely in ventricle. It occurs when atria become greatly dialated due to valvular heart disease.

Fibrilation : Fibrilation means a very high frequency of heart beat with incordinated contraction of cardiac muscle.

Angina pectoris

It is the cardiac pain that begins to appear whenever the load on the heart becomes to great in relation to the coronary blood flow, due to development of progressive constriction of the coronary arteries. It is usually felt beneath the upper sternum and is often also transferred to surface areas of the body, most often to the Lt. shoulder but also frequently to the neck and even to the side of the face or to the right arm and shoulder.

Treatment of angina pectoris :

1. Administration of vasodilator drugs.
   a. Nitro glycerine.
   b. Amyl nitrite gives immediate relief from the pain in acute anginal attack.
2. Blockage of the sympathetic nervous stimulation of the heart by propranolol.

Echocardiography

Wall movement and other aspects of cardiac function can be evaluated by echocardiography, a noninvasive technique that does not involve injections or insertion of a catheter. In echocardiography, pulses of ultrasonic waves, commonly at a frequency of 2.25 MHz, are emitted from a transducer that also

functions as a receiver to detect waves reflected back from various parts of the heart. Reflections occur wherever acoustic impedance changes, and a recording of the echoes displayed against time on an oscilloscope provides a record of the movements of the ventricular wall, septum, and valves during the cardiac cycle. When combined with Doppler techniques, echocardiography can be used to measure velocity and volume of flow through valves. It has considerable clinical usefulness, particularly in evaluating and planning therapy in patients with valvular lesions.

(Ref. Ganong 21th ed; Page-570)

Blood Pressure

Definition : It is the lateral pressure exerted by the moving colum of blood on the vessel wall per unit area (sq. mm) by its contained blood while flowing through it.

Blood pressure = Cardiac output x Peripheral resistance.

Importance of blood pressure

1. It is essential for the flow of blood through the circulatory tree.
2. It provides motive force for filtration at the capillary bed which is essential for -
   a. Tissue nutrition.
   b. Formation of urine
   c. Formation of lymph
   d. For venous return.

Lateral pressure

It is that pressure when force is exerted at right angles to the direction of flow at any point within a tube filled with a circulating fluid.

(Resistance is opposition to force)

Basal blood pressure

It is the lowest pressure necessary in main-taining blood flow sufficient for needs of the body.

Criteria for recording basal blood pressure :

i. The subject is in reclining state.
ii. At least 5-6 hours after last meal.
iii. After resting for at least 30-40 minutes in a comfortably warm room.
iv. A mind at possible ease.

Causal blood pressure

Any pressure that is recorded under ordinary circumstances of life is known as the causal blood pressure.

Types of blood pressure

1. *Systolic pressure :* It is the maximum pressure during systole.
   It is about : 100 - 140 mm of Hg,
   Average : 120 mm of Hg.
2. *Diastolic pressure :* It is the minimum pressure during diastole.
   It is about : 60 - 90 mm of Hg,
   Average : 80 mm of Hg.
3. *Pulse pressure :* It is the difference between systole and diastolic pressure.
   It is ablut 30 - 40 mm of Hg.
4. *Mean pressure :* It is the average pressure persists in the circulation. It is the diastolic pressure plus one third (1/3) of pulse pressue.
   It is about : 78-98 mm of Hg.
   Average : 96 mm of Hg.

Significance of different types of BP

1. *Systolic pressure :* It indicates-
   a. The extent of work done by heart.
   b. The force with which the heart is working.
   c. The degree of pressure which the arterial walls have to withstand.
   d. It increases during excitement, exercise, meals etc.
   e. It decreases while sleep, rest etc.
2. *Diastolic pressure*
   a. It indicates the constant load against which the heart works.
   b. Increased diastolic pressure indicates that heart is approching to failure
   c. It is the index of peripheral resistance.
3. *Pulse pressure :* It indicates the cardiac output.
4. *Mean pressure :* Mean pressure is the driving force for blood flow. It depends on cardiac output and peripheral resistance.

Physiological variation of blood pressure

1. *Age :*

Infant	: 60/30	mm of Hg
1 year	: 80/40	mm of Hg
3 years	: 100/60	mm of Hg
20 Years	: 120/80	mm of Hg
45 years	: 145/90	mm of Hg
70 years	: 170/95	mm of Hg

2. *Sex :* In female, the blood pressure is slightly lower (5 mm of Hg), cause is unknown. After menopause, it reaches male level.
3. *Build :* The systolic pressure is usually high in an obese person.
4. *Exercise :* In strenuous exercise, the systolic pressure rises,

even up to 180 mm of Hg. In moderate exercise, it slighly rises. The diastolic pressure is usually lower.

5. *Posture :* During standing, diastolic pressure is slightly higher; systolic pressure lower. In recumbent position, this condition is reversed.
6. *Diurnal variation :* During day time, pressure rises upto 2-O'clock and then there is a slight fall. In case of night workers, the blood pressure rises during morning.
7. *During sleep :* During deep sleep, there is fall of blood pressure by 15-20 mm of Hg.
8. *After meal :* Blood pressure is raised during digestion due to increased cardiac output up to 20 mm of Hg.
9. *Emotion & Excitement :* Raises systolic pressure considerably.
10. *Respiration :* There are fluctuations of blood pressure due to variations in stroke volume and peripheral resistance.

    At a normal respiratory rate, the blood pressure falls during most part of inspiration. At a slower respiratory rate, the blood pressure is slightly higher during inspiration.

N.B.

1. In adult, diastolic blood pressure and systolic blood pressure, should not be (persistently) over 90 and 140 mm of Hg (excepting in old persons).
2. Acute fall (shock) and rise (hypertension) of BP are dangerous. Blood pressure homeostasis is maintained by
   i. Neural : Neural control starts immediately (when ever there is destabilising of blood pressure homeostasis) and consists of reflexs (mainly baroreceptor) readjustments.
   ii. Fluid volume control mechanisms : Whereas fluid volume control takes a few hours to establish fully and consists of renin-angiotensin-aldosterone and ANP mechanisms.
3. Clinically sphygmomanometer is the instrument which is used to measure the blood pressure but the instrument is not wholly dependable.
4. In hypertension, drugs are aimed to restore the blood pressure homeostasis, influencing, eithre-
   i. The neural mechanism, or
   ii. The fluid volume readjustment.

Factors controlling blood pressure

The factors that maintain blood pressure may conveniently be discussed under two main headings -

A. *Cardiac output* : Cardiac output depends upon-
   i. Blood volume
   ii. Venous return
   iii. Force of contraction of heart.
   iv. Frequency of heart beat.

B. *Peripheral resistance* : Peripheral resistance depends upon-
   i. Elasticity of arterial wall
   ii. Velocity of blood
   iii. Viscocity of blood
   iv. State of lumen of blood vessels.

Factors influencing blood pressure

Factors influencing blood pressure are as follows :

1. *Peripheral registance :* Increased peripheral registance increases blood pressure. It depends on
   a. Elasticity of arterial wall
   b. Velocity of blood
   c. Viscosity of blood
   d. State of vessel lumen.
2. *Cardiac output :* It increases blood pressure. It depends on heart rate and stroke vloume. storke volume again depends on-
   i. *End systolic volume :*
      a. Force of cotraction
      b. Peripheral resistance
   ii. *End diastolic volume :*
      a. Venous return
      b. Diastolic period.
      c. Contraction of heart.
3. *Age :* Blood pressure rises with age.

Infant	:	60 / 30 mm of Hg.
Children	:	100 /60 mm of Hg
Adult	:	120 / 80 mm of Hg.
Old	:	145 / 90 mm of Hg.

4. *Sex :* 10 % less in female.
5. *Postures :* In recumbent position blood pressure is lower than in standing or sitting posture.
6. *Exercise :* It increases blood pressure.

Q. 00 **What is venous pressure?**

i. *Definition* : It is the pressure in the venous system.

ii. *Pressure at different sites* :
   1. In the venules : 12 -18 mm of Hg.
   2. Larger veins : 5.5 mm of Hg. (about)
   3. *Certral venous pressure* : Certral pressure is the pressure of the great veins at their entrance into the right atrium. It is about 4.6 mm of Hg. But flactuates with respiration & heart action.

      Gravitational effect :

      It increased by 0.77 mm Hg for each cm below the right atrium and also decreased by 0.77 mm of Hg for each cm above the right atrium.

4. The mean pressure at the anticubitul vein = 7.1 mm of Hg.

Measurement of blood pressure

Blood pressure is measured by -

1. *Direct method :* The artery is exposed and an arterial cannula of which one end is inserted directly into the lumen of the exposed vessel and the other end is connected to the U-shaped mercury manometer that show the actual blood pressure in mm of Hg.
2. *Indirect method :*
   i. Oscillatory
   ii. Palpatory : Can measure only sytolic pressure
   iii. Auscultatory : Can measure both systolic and diastolic.

Auscultatory method

1. *Site* : Brachial artery (Arm)
2. *Instrument :* Sphygmomanometer
   The instrument consists of an inflatable rubber bag covered by nondistensable envelope of cotton fabric, called the cuff. The cavity of the bag is connected with a mercury manometer and a hand pump. A small valve connected with a screw will allow the air to escape from the air bag.
3. *Principle :* The principle is to balance the air pressure against the brachial artery pressure. The air pressure is applied from a rubber bag connected with a hand pump and a mercury manometer to measure the air pressure.
4. *Method :* The instrument is kept at the level of the heart and the cuff is tied round the upper arm. The chest piece of a stethoscope is placed on the brachial artery, a little below the cuff. Pressure is raised to 200 mm of Hg and then gradually released. Variations of sounds are heard-
   i. *1st phase :* Sudden appearance of a *clear taping sound*. This indicates systolic pressure. It persists while the pressure falls through 15 mm of Hg.
   ii. *2nd Phase :* The tap sound is replaced by a *murmur* persisting for another 15 mm of Hg.
   iii. *3rd phase* : The murmur is replaced by a *clear loud* going sound lasting for the next 20 mm of Hg.
   iv. *4th phase* : The loud sound suddenly becomes *muffled* and rapidly begins to fade. This point indicates diastolic pressure.
   v. *5th Phase :* Disappearance of all sounds.

Korotkoff sound

Blood flow through the smooth blood vessel, normally provides no sound, but if the brachial artery is partially occluded by inflated cuff then blood pours out in jet into the open vessel beyond the cuff, and gives rise to terbulance of flow which sets up vibration and produces sound called Korotkoff sound. It has four different stages.

1. *Tapping sound :* At the point at which systolic pressure in the artery just exceeds the cuff pressure, a spurt of blood passes through with each heartbeat and, synchronously with each beat, a tapping sound is heard below the cuff. The cuff pressure at which the sounds are first heard is the systolic pressure.
2. *Loud sound :* On decreasing the pressue (10 mm of. Hg) the sound become loud.
3. *Dull sound :* Further decreasing the pressure (15 mm of Hg.) the sound become dull.
4. *Muffle sound :* Further decreasing the pressure (15 mm of Hg) the sound become muffled and gradually disappears. The point at which the muffled sound start is diastolic pressure (British) or disapper's is diastolic pressure (American).

The diastolic pressure in resting adults correlates best with the pressure at which the sound disappears. However in adults after exercise and in children, the diastolic pressure correlates best with the pressure at which the sounds become muffled. This is also true in diseases such as hyperthyroidism and aortic insufficiency.

(Ref. Ganong 22th edition; page-589)

Turbulence

Turbulent flow means that the blood flows cross wise in the vessel as well as along the vessel, usually forming whorls in the blood called eddy currents.

When the rate of blood flow becomes too great or when it passes by an obstruction in a vessel or when it passes over a rough surface, the flow may then become turbulent rather than streamline.

(Ref. Guyton 11th edition)

Laminar flow

When blood flows through a smooth vessel each layer of blood maintains same distance from the wall. The central portion of blood remains in the centre of the vessel. This type of flow is called laminar flow or streamline flow.

Q. ***Why blood pressure increases in old age, exercise and pregnancy?***

1. ***In old age :*** Blood pressure increases due to -
   a. Athero-sclerotic change in the artery and its wall become thick.
   b. Artery become stiff & its elasticity decreases.
2. ***In exercise :*** Blood pressure rises due to -
   a. Increased venous return.
   b. Increased metabolic activity & much energy & O_2 is required.
   c. Increased heart rate & cardiac out put due to increased venous return.

3. ***In pregnancy :*** Blood volume both plasma & corpuscles increase which increases cardiac out put, thus blood pressure is raised.

Q. ***Which is more important, the systolic or diastolic pressure ?***

Ans. Diastolic pressure is the level at which the heart is pumping blood. If the diastolic pressure is raised, heart is doing more work, Therefore it may be hypertrophied, leading to heart failure. So, diastolic pressure is more important than systolic pressure.

Hypertension

Definition : Hypertension is a clinical condition characterized by persistance rise of blood pressure above the normal range in respect of age and sex. Hypertension occurs when diastolic pressure is greater than 90 mm of Hg and systolic pressure is above 150 mm of Hg.

Type :

Hypertension is of two types -
1. Primary or essential hypertension.
2. Secondary hypertension.

Essential hypertension : When arterial blood pressure persistently exceeds 150/90 or 160/100 mm of Hg. Its cause is unknown. It is of two types -

a. *Benign form* : In the early stages the hypertension is moderate, e.g. 210/110 mm of Hg. The blood pressure, specially the systolic, fluctuates considerably; during sleep or emotional and physical rest, the pressure is normal; in states of stress the pressure rises to excessive levels. Later the hypertenstion becomes fixed in the abnormal range and can not be reduced to normal by rest or sedatives. After a period which may vary from a few years to 20 years : death occurs from heart failure, vascular accedents (haemorrhage or thrombosis), or renal failure.

b. *Malignant form* : The condition is so named because death occurs within months to 2 years of its first recognition. The BP is much higher than in the benign form e.g 260/150 of Hg.

Secondary hypertension : It is due to other diseases, as renal diseases, phaeochromo- cytoma, by excess secretion of glucocorticoids or aldosterone, by coarctation of aorta.

(Ref. Wrights 13th page 152-153)

Vloume loading hypertension : Hypertension occurs due to excess extracellular fluid volume. It is due to excess salt intake or salt retension from kidney.

Vasoconstrictor hypertension : It is due to continuous infusion of vasoconstrictor agent into blood or by excessive secretion of vasoconstrictor from endocrine gland. The vasoconstrictors are-

i. Angiotensin-II
ii. Norepinephrine
iii. Epinephrine.

Regulation of Blood Pressure

Two major types of arterial pressure control system in the body:
1. Nervous mchanism
2. Humoral mechanism.

1. **Nervous mechanism** : Has two different types-
   i. ***Short terms regulation :*** Occurs within seconds to minites.
      A. *Mechanism occurs within seconds :*
         a. Baroreceptor feed back mechanism,
         b. Chemoreceptor feed back mechanism.
         c. Central nervous system ischemic mechanism.
      B. *Mechanism occurs within minutes :*
         a. Renin angiotensin vasoconstrictor mechenism.
         b. Capillary fluid shift mechanism.
         c. Stress relaxation changes in vasculature.
   ii. ***Longterm regulation :***
      a. Renal body fluid mechanism.
      b. Renin angiotensin mechanism.

2. **Humoral regulation**
   a. Epinephrin- norepinephrin mechanism
   b. Vasopressin vasoconstrictor mechanism (ADH)
   c. Renin angiotensin aldoterone mechanism.

(Ref. Guyton & Hall-11th edittion)

Comparison between short-term and long-term regulation of blood pressure :

Short term regulation	*Long term regulation*
i. Rapid onset (seconds to minutes)	i. Slow onset (hours to days)
ii. Controls blood pressure for short duration	ii. Controls blood pressure for long duration
iii. It cannot bring the blood pressure all the way back to normal.	iii. It brings the BP all the way back to normal.

Reflexes & control mechenisms in cardiovascular system

Cardiovascular reflexes are the major instruments by which
i. Heart rate
ii. Blood pressure
iii. Blood flow are maintained and readjusted to the needs of the body.

Each reflex, officially should have-

i. Afferent limb
ii. Center (eg.VMC, cardiac center etc), and
iii. Efferent limb.

However, owing to extensive interconnections between them it is no longer very fashionable to call them individual cardiac centers as they do not work independently. Most reflexes operate principally via the sympathetic system al though the vagus has considerable influence on the heart (but not on the blood vessels in general). Both sympathetic and para-sympathetic discharge tonically. Most efferent sympathetics are vasoconstrictors and withdrawal of these tonic vasocontrictor activity of the sympathetic leads to vasodilation (and also bradycardia). However, sympathetic vasodila tors also exist. The NT for vasoconstrictors are noradrenalin but the NT for sympathetic vasodilators are Ach.

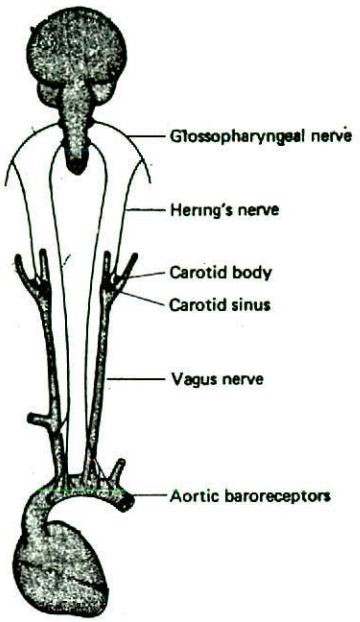


Fig. 6-12. *The baroreceptor system.*

Baroreceptors mechanism

Baroreceptors : The baroreceptors are stretch spray-type nerve endings (receptors) in the walls of the arteries; they are stimulated when stretched.

Sites/locations of baroreceptors :

1. Baroreceptors are extremely abundant-
   i. In the wall of each internal carotid artery slightly above the carotid bifurcation, an area known as the *carotid sinus.*
   ii. In the wall of the aortic arch.
2. A few baroreceptors are located in the wall of every large artery of the thoracic and neck regions.

Response of the baroreceptors to pressure :

1. *Carotid sinus receptors* : They are not stimulated at all by pressures between 0 and 50 to 60 mm of Hg, but above these levels, they respond progressively more rapidly and reach a maximum at about 180 mm of Hg.
2. *Aortic baroreceptors* : The responses of these are similar to those of the carotid receptors except that they operate, in general, at pressure levels about 30 mm Hg higher.

In the normal operating range of arterial pressure, around 100 mm Hg, even a slight change in pressure causes a strong change in baroreflex signals to readjust the arterial pressure back toward normal. Furthermore, the baroreceptors *respond much more to a rapidly changing pressure* than to a stationary pressure.

Baroreceptor control system of blood pressure :

1. Baroreceptors are stimulated when they are stretched due to increase arterial pressure. These signals are transmitted from each carotid sinus through the very small *Hering's nerve* to the glossopharyngeal nerve and then to the *tractus solitarius* in the medullary area of the brain stem. Signals from the arch of the aorta are transmitted through the vagus nerves also into the same area of the medulla.
2. After the baroreceptor signals have entered the tractus solitarius of the medulla, secondary signals *inhibit the vasoconstrictor center.* The net effects are-
   i. *Vasodilatation* of the veins and arterioles throughout the peripheral circulatory system.
   ii. *Decreased heart rate* and *strength of heart contraction.*

   Therefore, excitation of the baroreceptors by pressure in the arteries reflexly *causes the arterial pressure to decrease* because of both a decrease in peripheral resistance and a decrease in cardiac output.

   Conversely, *low pressure has opposite effects*, reflexly causing the pressure to rise back toward normal.

(Ref. Guyton & Hall-11th edition: Page 209)

Baroreceptor

Increase arterial pressure
↓
Arterial baroreceptors stimulation
↓

↓	↓
Vagus nerve	Glossopharyngeal nerve
↓	↓
Cardioinhibitory centre stimulated	Vasomotor centre inhibited
↓	↓
Increase parasympathetic discharge to SA and AV node and ventricular muscle	Venodilatation Vasodilatation
↓	
Decrease heart rate Decrease myocardial contractility	↓

↓
→ Decrease cardiac output
Decrease total peripheral resistance
↓
Decrease arterial pressure.

Pressure buffer system

Nerves from the baroreceptors are called buffer nerves. Baroreceptor system opposes an increase and a decrease in the arterial pressure; so, it is often called a pressure buffer system.

Merits and demerit of baroreceptor regulation :

i. Merits :
   a. Rapidly acting blood pressure control mechanism
   b. A diurnal variation of blood pressure is corrected by baroreceptor mechanism.

ii. *Demerit* :
   a. Very short period of action
   b. Acts only in response to changing pressure, not to static.

Carotid Sinus & Aortic Arch

The carotid sinus is a small dilation of the internal carotid artery just above the bifurcation of the common carotid into external and internal carotid branches. Baroreceptors are located in this dilation. They are also found in the wall of the arch of the aorta. The receptors are located in the adventitia of the vessels. They are extensively branched, knobby, coiled, and intertwined ends of myelinated nerve fibers that resemble Golgi tendon organs. Similar receptors have been found in various other parts of the large arteries of the thorax and neck in some species. The afferent nerve fibers from the carotid sinus and carotid body form a distinct branch of the glossopharyngeal nerve, the carotid sinus nerve , but the fibers from the aortic arch form a separate distinct branch of the vagus only in the rabbit. The carotid sinus nerves and vagal fibers from the aortic arch are commonly called the buffer nerves.

(Ref. Guyton & Hall-11th edition; Page 209)

Control of Arterial Prssure by the Carotid and Aortic Chemoreceptors- Effect of Oxygen Lack on Arterial Pressure : Closely associated with the baroreceptor pressure control system is a chemoreceptor reflex that operates in much the same way as the baroreceptor reflex except that chemoreceptors, instead of stretch receptors, initiate the response.

The chemoreceptors are chemosensitive cells sensitive to oxygen lack, carbon dioxide excess, or hydrogen ion excess. They are located in several small organs 1 to 2 millimeters in size : two carotid bodies, one of which lies in the bifurcation of each common carotid artery, and several aortic bodies lies adjacent to the aorta. The chemoreceptors excite nerve fibers that, along with the baroreceptor fibers, pass through Hering's nerves and the vagus nerves into the vasomotor center.

Each carotid or aortic body is supplied with an abundant blood flow through a small nutrient artery, so that the chemoreceptors are always in close contact with the arterial blood. Whenever the arterial pressure falls below a critical level, the chemoreceptors become stimulated because of diminished blood flow to the bodies and therefore diminished availability of oxygen as well as excess buildup of carbon dioxide and hydrogen ions that are not removed by the slow flow of blood.

The signals transmitted from the chemoreceptors into the vasomotor center excite the vasomotor center, and this elevates the arterial pressure. This reflex helps to return the arterial pressure back toward the normal level whenever it falls too low.

The chemoreceptor reflex is not a powerful arterial pressure controller in the normal arterial pressure range because the chemoreceptors themselves are not stimulated strongly by pressure changes until the arterial pressure falls below 80 mm Hg. Therefore, it is at the lower pressures that this reflex becomes especially important to help prevent still further fall in pressure.

(Ref. Guyton & Hall-11th edition; Page 211)

Schemetic representation of the chemoreceptors mechenism of blood presssure control :

Decreased arterial pressure
↓
Decreased blood supply to chemoreceptors
↓
Hypoxia, excess CO_2 (local) and excess H^+ (local)
↓
Chemoreceptors are stimulated
↓
Signals go to vasomotor area and causes excitation of the vasomotor area
↓
Vasoconstriction (i.e increased total peripheral resistance)
Increased myocardial contractility
↓
Elevation of arterial pressure.

Central nervous system ischemic response. Control of arterial pressure by the brain's vasomotor center in response to diminished brain blood flow :Most nervous control of blood pressure is achieved by reflexes that originate in the baroreceptors, the chemoreceptors, and the low-pressure receptors, all of which are located in the peripheral circulation outside the brain. When blood flow to the vasomotor center in the lower brain stem becomes decreased enough to cause nutritional deficiency, that is, to cause cerebral ischemia, the neurons in the vasomotor center itself respond directly to the ischemia and become strongly excited. When this occurs, the systemic arterial pressure often rises to a level as high as the heart can possibly pump. This effect is believed to be caused by failure of the slowly flowing blood to carry carbon dioxide away from the vasomotor center, the local concentration of carbon dioxide then increases greatly and has an extremely potent effect in stimulating the sympathetic nervous control areas in the brain's medulla. It is possible that other factors such as the build up of lactic acid and other acidic substances, also contribute to the marked stimulation of the vasomotor center and to the elevation in pressure. This arterial pressure elevation

in response to cerebral ischemia is known as the central nervous system ischemic response, or simply CNS ischemic response.

The magnitude of the ischemic effect on vasomotor activity is tremendous : it can elevate the mean arterial pressure for as long as 10 minutes sometimes to as high as 250 mm Hg. The degree of sympathetic vasoconstriction caused by intense cerebral ischemia is often so great that some of the peripheral vessels become totally or almost totally occluded. The kidneys, for instance, often entirely cease their production of urine because of arteriolar constriction in response to the sympathetic discharge. Therefore, the CNS ischemic response is one of the most powerful of all the activators of the sympathetic vasoconstrictor system.

(Ref. Guyton & Hall-11th edition; Page 212)

Schematic representation of the central nervous system ischemic mechanism of blood pressure control :

Decreased arterial pressure
↓
Decreased cerebral blood flow
↓
Cerebral ischemia
↓
Decreased blood flow to vasomotor center
↓
Accumulation of CO_2, lactate and other metabolites in the vasomotor center
↓
Direct stimulation of vasomotor center (Sympathetic nervous control area)
↓
Vasoconstriction (i.e increased total peripheral resistance)
↓
Increased arterial pressure
↓
Increased cerebral blood flow.

Vasopressin mechenism

Decrease circulatory volume i.e hypovolaemia → Decrease blood pressure ↓

Osmoreceptor in the hypothalamus are stimulated → **Stimulate vasopressin sectretion from the posterior pituitary** ↓

Increased plasma osmolality ↑

Anti-diuresis (i.e. decrease urine volume) ↓

Vasoconstiction ↓

↓
Increase blood volume ↓ — Increase total peripheral resistance ↓
Increase cardiac output ↓ — ↓
↓
Increase arterial pressure.

Norepinephrine vasoconstriction mechanism

Decreased arterial pressure
↓
Sympathetic stimulation
↓
↓
Stimulation of adrenal medulla
↓
Catecholamine secretion
↓ — ↓
Vasoconstriction — Increase total peripheral resistance
↓ — ↓
Increase arterial pressure.

Renal body fluid mechanism

When blood pressure rises, causes kidney out put of water and salt increases. This inturn decreases extracellular fluid volume and decreases blood volume. The decreased blood vloume decreases pumping action of heart which return arterial blood pressure back to normal. Conversely, when blood pressure low, the output of water and salt by kidney decreases that increases ECV and ultimately blood volume. The increased blood volume increases mean circulating filling pressure that increases venous return then cardiac out put. This increased cardiac output then increases blood pressure.

↑ B.P
↓
↑ Output by Kidney
↓
↓ E.C.F. volume
↓
↓ Blood volume
↓
↓ Pumping action of heart
↓
↓ B.P

Renin-Angiotensin system

Its role in pressure control and hypertension : Aside from the capability to control pressure through changes in extracellular fluid volume, the kidneys have another powerful mechanism for cotrolling pressure. It is the renin-angiotensin system.

Renin is a small protein enzyme released by the kidneys when the arterial pressure falls too low. In turn, it raises the arterial pressure in several ways, thus helping to correct the initial fall in pressure.

Components of the renin-angiotensin system: Renin is synthesized and stored in an inactive form called prorenin in the juxtaglomerular cells (JG cells) of the kidneys. When the arterial pressure falls, intrinsic reactions in the kidneys themselves cause many of the prorenin molecules in the JG cells to split and release renin. Most of the renin enters the blood and then passes out of the kidneys to circulate throughout the entire body. However, small amount of renin do remain in the local fluids of the kidney and initiates several intrarenal functions.

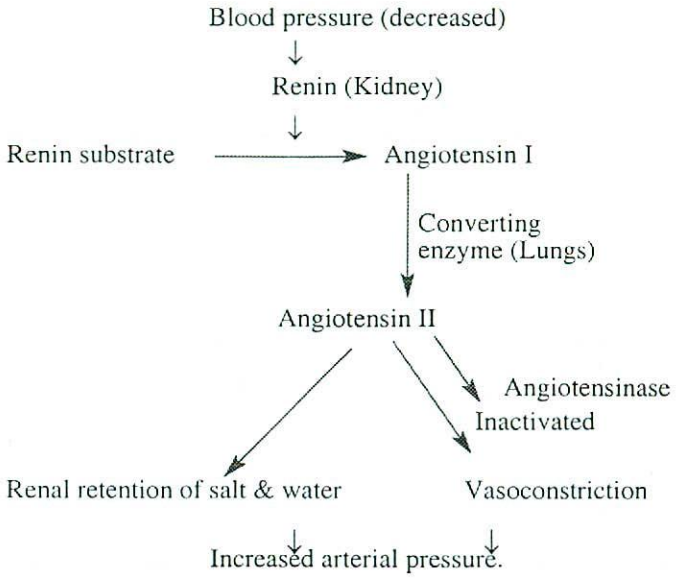


Diagram. Angiotensin Vasoconstriction mechanism for arterial pressure control.

Renin itself is an enzyme not a vasoactive substance. It acts enzymatically on another plasma protein, a globulin called renin substrate (or angiotensinogen) to release a 10 amino acid peptide, angiotensin I. Angiotensin I has mild vasoconstrictor properties but not enough to cause significant functional changes in circulatory function. The renin persists in the blood for 30 minutes to 1 hour and continue to cause formation of angiotensin I during this entire time.

Within a few seconds after formation of the angiotension I, two additional amino acids are split from it to form the 8 amino acid peptide angiotensin II. This conversion occurs almost entirely during the few seeonds while the blood flows through the small vessels of the lungs, catalyzed by the enzyme *converting enzyme* that is present in the endothelium of the lung vessels.

Angiotensin II is an extremely powerful vasoconstrictor, and it has other effects as well that affect the circulation. It persists in the blood only for 1 or 2 minutes because it is rapidly inactivated by multiple blood and tissue enzymes collectively called angiotensinase.

During its persistence in the blood, angiotensin II has two principal effects that can elevate arterial pressure. The first of these, vasoconstriction, occurs rapidly. Vasoconstriction occurs intensely in the arterioles and to considerably less extent in the veins. Constriction of the arterioles increases the peripheral resistance, thereby raising the arterial pressure. Also, the mild constriction of the veins promotes increased venous return of blood to the heart, thereby helping the heart pump against the increasing pressure.

Angiotensin causes the kidneys to retain both salt and water in two ways-

1. Angiotensin acts directly on the kidneys to cause salt and water retention.
2. Angiotensin cause the adrenal glands to secrete aldosterone, and the aldosterone inturn increases salt and water reabsorption by the kidney tubules (Cortical collecting tubules).

1. ***Mechanisms of the direct renal effects of angiotensin to cause renal retention of salt and water :*** Angiotensin has several intrarenal effects that make the kidneys retain salt and water. Probably the most important is to constrict the renal blood vesels, thereby diminishing blood flow through the kidneys. As a result, less fluid filters through the glomeruli into the tubules. Also the slow flow of blood in the peritubular capillaries reduces their pressure, which allows rapid osmotic reabsorption of fluid from the tubules. Thus, for both of these reasons, less urine is excreted. In addition, angiotensin has a moderate effect on the tubular cells themselves to increase tubular reabsorption of sodium and water. The total result of all these effects is significant, sometimes decreasing urine output fourfold to sixfold.

2. ***Stimulation of aldosterone secretion of angiotensin and the effect of aldosterone in increasing salt and water retention in the kidneys.***

   Angiotensin is also one of the most powerful controllers of aldosterone secretion. Therefore, when the renin-angiotensin system becomes activated, the rate of aldosterone secretion usually increases at the same time. One of the most important functions of aldosterone is to cause marked increase in sodium reabsorption by the kidney tubules (cortical collecting tubule), thus increasing the extracelluar fluid sodium. This then causes water retention, thus increasing the extracellular fluid volume and leading secondarily to still more long term elevation of the arterial pressure.

   Both the direct effect of angiotensin on the kidney and its effect acting through aldosterone are important in long-term arterial pressure control. However, research in our own laboratory has suggested that the direct effect of angiotensin on the kidneys is perhaps three or more times as potent as the indirect effect acting through aldosterone even though the indirect effect is the one most widely known.

(Ref. Guyton & Hall-11th edition; Page 223, 224)

Bain Bridge reflex

Rise of pressure in the ritght atrium stimulates the baroreceptors present in its wall. The impulse passes through vagus nerve and reflexly stimulates the H. R & strengh of conraction.

(Ref. Guyton & Hall-11th edition)

Summary of

The integrated, multifaceted system for arterial pressure regulation

Arterial pressure is regulated not by a single pressure controlling system but instead by several interrelated systems each of which performs a specific function. For instance, when a person bleeds severely so that the pressure falls suddenly, two problems confront the pressue control system. The *first* is the survival, that is, to return arterial pressure immediately to a high enough level that the person can live through the acute episode. The *second* is to return the blood volume eventually to its normal level so that the circulatory system can re-establish full normally, including return of the arterial pressure all the back to its normal value, not merely back to a pressure level required for survival.

These mechenisms can be divided into three groups :

1. Those that react rapidly, within seconds or minutes. They are-
   i. Baroreceptor feedback mechenism
   ii. Central nervous system ischemic mechenism
   iii. Chemoreceptor mechenism.
2. Those that respond over an intermediate time period, minutes or hours.
   i. Renin angiotensin vasoconstrictor mechenism
   ii. Stress relaxation of the vasculature
   iii. Shift of fluid through the tissue capillary walls in and out of the circulation to readjust the blood volume as needed.
3. Those that provide long-term arterial pressure regulation, days, months, years.
   i. Renal-blood volume pressure control mechenism (which is the same as the renal-body fluid pressure control mechenism.

(Ref. Guyton & Hall-11th edition; Page 230)

Rapidly acting pressure control mechenism (acting within seconds or minutes) : The rapidly acting pressure control mechenisms are almost entirely acute nervous reflexes or other nervous responses. After any acute fall in pressure, as might be caused by severe haemorrhage, the nervous mechenisms combine-

1. To cause constriction of the veins and provide transfer of blood to the heart.
2. To cause increased heart rate and contractility of the heart and provide greater pumping capacity by the heart.
3. To cause constriction of the peripheral arterioles to impede the flow of the blood out of the arteries.

All these effects occur instantly to rise the arterial pressure back into a survival range.

When the pressure rises suddenly too high, as might occur in response to a drug or extreme, rapid overadministration of a blood transfusion, the same mechenisms operate in the reverse direction, again returning the pressure back toward the normal range.

(Ref. Guyton & Hall-11th edition; Page 230)

Pressure control mechenisms that act after many minures : These mechenisms become mostly activated within 30 minutes to several hours.Their effects can last for long periods, days if necessary. During this time, nervous mechenisms usually fatigue and become less and less effecive, which explains the importance of these non-nervous intermediate time pressure control measures.

i. ***The stress-relaxation mechenism*** is demonstrated by the following example : When the pressure in the blood vessels becomes too high, they become stretched keep on stretching more and more for minutes or hours; as a result, the pressure in the vessels falls toward normal. This continuing stretch of the vessels, called stress-relaxation, can serve as an intermediate-term pressure 'buffer'.

ii. The ***capillary fluid shift mechenism*** means simply that any time the capillary pressure falls too law, fluid is absorbed by capillary osmosis from the tissues into the circulation, thus building up the blood volume and increasing the pressure in the circulation. Conversely, when the capillary pressure rises too high, fluid is lost out of the circulation into the tissues, thus reducing the blood volume as well as all the pressures throughout the circulation.

(Ref. Guyton & Hall-11th edition; Page 230)

Long term mechenisms for arterial pressure regulation : It takes a few hours to show sigficant response. It eventually develops a feedback gain for control of arterial pressure equal to infinity. This means that this mechenism can eventually return the arterial pressure all the way back, not merely partway back, to that pressure level that provides normal output of salt and water by the kidneys.

Many factors can affect the pressure-regulating level of the renal-body fluid mechenism. One of these is aldosterone. A decrease in arterial pressure leads within minutes to an increase in aldosterone secretion, and over the next hour or days, this plays an importasnt role in modifying the pressure control characteristics of the renal-body fluid mechenism. Especially important is the interaction of the renin-angiotensin system with the aldosterone and renal fluid mechenisms.

Thus the arterial pressure control begins with the saving measures of the nervous pressure controls, then continues with

the sustaining characteristics of the intermediate pressure controls, and finally, is stabilized at the long-term pressure level by the renal-body fluid mechenism. This long- term mechenism in turn has multiple interactions with the renin-angiotensin-aldosterone system, the nervous system, and several other factors that provide special presssure control capabilities for special purposes.

(Ref. Guyton & Hall-11th edition; Page 231)

Applied :

Carotid sinus syndrome : Strong pressure on neck over the bifurcation of carotid artery excites the baroreceptors and causes fall of blood pressure upto 20 mm of Hg in normal person. In old person particularly after the formation of calcified arteriosclerotic plaques in the carotid artery, neck pressure (even light collars) over the carotid sinus produces marked fall in arterial pressure causing fainting of the person, such effect is called carotid sinus syndrome.

(Ref. Guyton & Hall-11th edition; Page 148)

Stokes Adams syndrome : When AV block occurs that is, when the cardiac impulse fails to pass from the atria into the ventricles through the AV nodal and bundle system - the atria continue to beat at the normal rate of rhythm of the sinus node, while a new pacemaker develops in the purkinje system of the ventricles and drives the ventricular muscle at a new rate somewhere between 15-40 beats per minute. After a sudden block, the Purkinje system does not begin to emit its rhythmical impulses until 5 to 30 seconds later because, before the blockage, the Purkinje fibers had been "overdriven" by the rapid sinus impulses and, consequently, are in a suppressed state. During these 5 to 30 seconds, the ventricles fail to pump blood, and the person faints after the first 4 to 5 seconds because of lack of blood flow to the brain. This delayed pickup of the heartbeat is called Stokes Adams syndrome. If the delay period is too long it can lead to death.

(Ref. Guyton & Hall-11th edition; Page 121)

Extrasystole or premature beat or ectopic beat

Definition : A premature contraction is a contraction of the heart prior to the time that normal contraction would have been expected. This condition is frequently called extrasystole or premature beat.

Causes : Most premature contractions results from ectopic foci in heart; and the probable causes of ectopic foci are-

i. Local areas of ischemia.
ii. Small calcified plaques at different points in heart, which press against the adjacent cardiac muscle, so that some of the fibres are irritated.
iii. Toxic irritation of the AV node, purkinje system or myocardium caused by drugs, nicotine or caffine.
iv. Mechanical irritation during cardiac catheterization.

(Ref. Guyton & Hall-11th edition; Page 150)

*In **CVS shock***, the cardiac output is not sufficient to meet the demands. Nature's compensatory mechanisms consist mainly of neural (baroreceptor reflex etc), fluid shift and renin angiotensin mechanism.

Heart failure may be seen as pump failure and the cardiac output is insufficient to the need. Compensatory mechanisms include a. Frank starling's law b. Sympathetic overactivity (due to baroreceptor and other reflexes). Pump failure is aggravated because of the operation of Laplace's law.

The ***murmurs*** of valvular disease,logically, can occur even if the critical value of Reynold's number is not exceeded , although exercising the patient increases the propensity of turbulence and murmur.

Common sites of ***heart blocks*** are AVN, bundle branch (right/left). Sick sinus syndrome affects the SAN.

Atrial fibrillation is a chronic condition whereas ventricular fibrillation usually kills instan taneously.

Vascular system

Definition : The vascular system is a closed system of conduits that carry blood from the heart to the tissues and back to the heart.

The forward motion of blood is due to :

i. Pumping action of the heart.
ii. Elastic recoil of the vessels during diastole
iii. Compression of the veins by skeletal muscle during exercise
iv. Negative pressure in the thorax during inspiration.

Classification of blood vessels

Blood vessels can be classified in two ways :

1. Anatomically.
2. Functionally.

1. ***Anatomical classification :***

   A. *Artery :* Vessels which carries oxygenated blood (except pulmonary artery) is called artery. These are -
      i. Large arteries : Aorta and its branches.
      ii. Medium sized arteries : Brachial, Radial, Popleteal etc.
      iii. Small arteries : Arterioles, Terminal arterioles.
      iv. Capillaries or sinusoids.

   B. *Veins:* Vessels which carries deoxygenated blood (except pulmonary veins) is called veins. These are :
      i. Large veins : Superior and Inferior vena-cava and their large tributeries.
      ii. Medium sized vein : Brachial, Tibial veins etc.
      iii. Small veins, Venules etc.

2. **Functional classification of vessels**

a. ***Windkesel (distribution vessels)*** : The large vessels which arises from heart and distributes blood to the whole body, e.g arteries upto the arteriolar level. Percentage of elastic fibers high; elastic recoil ++.

Function : Windkessel effect; vis a tergo.

Applied physiology : Arteriosclerosis →loss of Windkessel.

Effect : Systolic blood pressure increase but diastolic blood pressure falls.

b. ***Resistance vessels*** : The vessels which control blood flow by exerting resistance on the vessel wall, e.g arterioles, terminal arterioles.

Elastic fibers almost nil; percentage of smooth muscles (++).

Function : Seat of peripheral resistance. Smooth muscles are strongly influenced by sympathetic nerves, noradrenalin, adrenalin.

Appllied physiology : Essential hypertension → narrowing of lumen → Diastolic blood pressure increased .

Distribution of vascular resistance :

1. Small arteries & arterioles : 47 %
2. Capillaries : 27 %
3. Arteries : 19 %
4. Veins : 7 %.

(Ref. Colour Atlas of physiology)

c. ***Exchange vessels*** : The vessels which are concerned with the exchange of gases, nutrients, vitamins and hormones between the blood and the body fluid, e.g capillaries. Single layer of endothelium.

Function : Exchange of nutrients, gases and waste products.

d. ***Capacitance vessels*** : The vessels which contains a large volume of blood e.g veins and venacva.

Wall is thicker than venules but much thinner than aorta.

Function : Holds extra fluid (acts as a reservior) without BP elevation.

Venules : Wall is only slightly thick.

General structure of the vascular tree

The aorta and big arteries has three coats :

i. Tunica adventitia
ii. Tunica media
iii. Tunica intima. (i.e tunic = coat).

i. Tunica *intima* : Tunica intima is the innermost coat. Internally it has a lining of single layer of epithelium called the (vascular) endothelium. This layer is very smooth and silky in health. This layer, therefore, is in contact with the blood. External to the endothelial layer, lies, mainly some elastic fibers and this layer of elastic fibers is called, the *lamina propria.*

The lamina propria is externally bounded by a layer of elastic fibers called the fenestrated membrane.

Therefore tunica intima = the endothelial layer + lamina propria +fenestrated membrane.The region of lamina propria is also called the subendothelial region.

In the subintimal layer, cholesterol and other lipid materials are first deposited in the disease called atherosclerosis.

ii. *Tunica media* : External to the fenestrated membrane lies the *tunica media.* In tunica media, there are smooth muscles as well as good deal of elastic fibers. The layer is fairly thick .

iii. *Tunica adventitia :* External to the tunica media, lies the layer called *tunica adventitia.* It consists of collagenous fibers mainly.

The above mentioned histological structure is typical of the Windkessel vessels (aorta and the big arteries). In smaller arteries the picture changes to some extent.

Differences from large arteries or windkessel vessel

1. ***Smaller arteries*** : The amount of elastic fibers, both in the tunica intima and tunica media are much less and the proportion of smooth muscular tissue in the tunica media increases.
2. ***Arterioles*** : The elastic fibers have disappeared from the media and the tunica media consists only of smooth mucles.
3. ***Capillaries*** : There is no adventitia or media. The intima consists only a layer of endothelium standing on a basement membrane.
4. ***Veins***
   i. Walls thinner than arteries.
   ii. Elasticity is very low compared to the arteries.
   iii. Smooth muscle content is also very low.

Vascular smooth muscle

Characteristics :

i. *Position* : Smooth muscles of media are placed circularly round the vesscls. Therefore, when they contract, the diameter of the vesscls is reduced.

ii. *Nerve supply* :
Sympathetic fibers (nor adrenalin)
Receptor : Alpha receptor.

Sympathetic stimulation → release of noradrenalin → combine with alpha receptor → contraction (Sympathetic fibers exert a tonic effect even at rest).

N.B. Alpha receptor can also combine with adrenalin (epinephrine) and phenyl epinephrine; which are also, therefore powerful vasoconstrictors.

*Phenoxybenzamine and dibenamine produce alpha blocking and therfore cause powerful vasodilatation and fall of arterial blood pressure.

3. Sympathetic fibers exert a tonic effect even at rest.
4. Some arterioles (skeletal muscles) contain β_2 receptors → causes vasodialtation. Similarly there is histaminergic receptors.
5. *Cholenergic receptors* : Presents in some smooth muscles which can combine with acetylcholine (Ach) → vasodilatation → fall of blood pressure (these cholenergic receptors, strengly enough are not attached with any nerve fibers).
6. *Others* :
   a. Smooth muscles can be stimulated or inhibited by number of agents :
      i. local O_2 tension
      ii. Lactic acid
      iii. Adenosine
      iv. Histamine
      v. Bradykinin
      vi. Prostaglandins
      vii. Anti-diuretic hormone (ADH) and others.
   b. *Vasomotor tone* : Indicates the degree of tone of the vascular smooth muscle. Thus when the vasomotor tone is high, the vessels are narrowed and vice versa.
   c. *Vasoactive agents* : Substances which can act on vascular smooth muscles.
   d. *Vasoactive amines* : Vasoactive agents which are amine in chemical nature (e.g histamine, 5 hydroxytryptamine).
   e. *Vasopressor agent* : Is a substance that causes contraction of vascular smooth muscle e.g Nor-adrenalin.

Effect of Sympathetic nerve on vascular smooth muscles :

1. Arterioles of some region constricts → e.g Splanchnic and cutaneous.
2. Arterioles of some region dilates → Coronary muscles, skeletul muscles.
3. Arterioles of some other resion are not affected → e.g brain.

* Sympathetic nerve (Stimulation) thus causes redistribution of blood supply.

Capillaries

A. *Diameter* :
   i. At the arterial end : 5mm
   ii. At the venous end : 9 mm

B. *Total area of all the capillary walls in the body* :
Exceeds 6300 square meter (in adalt).

C. ***Structure*** :
Varies from organ to organ

A. *Types of endothelium* :
   i. Continious : This type endothelium present in brain (excluding circumventricular organs), skin, skeletal muscle, lungs, heart.
   ii. Fenestrated : This type endothelium present in gastro-intestinal tract (intestinal mucosu), glomerulus in kidney.

B. *Structure of endothelium in various organ* :
   i. *Muscles (skeletal, cardial & smooth muscle)* : The junction between the endothelial cells permit the passage of molecules up to 10 nm in diameter (vesicular trnsport).
   ii. *Brain* : Tight junction present. Non fenestrated. They permit the passage of small molecules.
   iii. *Endocrine glands (most), intestinal villi and parts of the kidneys* : Fenestration (20-100 mm in diameter) present that permit the passage of relatively large molecules and make the capillaries porous.

iv. *Liver* : Endothelium is discontinious. There are large gaps between endothelial cells that are not closed by membranes (600-3000 nm in diameter).

N.B. Capillaries & post capillary venules have pericytes outside the endothelial cells. They are contractile & release a wide variety of vasoactive agents. They also synthesize and release constituents of the basement membrane & extra cellular matrix.

Function : Regulation of flow through the junctions between endothelial cells, particulary in the presence of inflammation.

Characteristics of various types of blood vesels in humans :

Vessel diameter	*Lumen thickness*	*Wall*	*All Vessels of Each Type*	
			Approximate total cross sectional area (cm^2)	*Percentage of blood volume contained)*
Aorta	*2.5 cm*	*2 mm*	*4.5*	2
Artery	0.4 cm	1 mm	20	
Arteriole	30 μm	20 μm	400	1

Vessel diameter	Lumen thickness	Wall	All Vessels of Each Type: Approximate total cross sectional area (cm^2)	All Vessels of Each Type: Percentage of blood volume contained)
Capillary	5 μm	1 μm	4500	5
Venule	20 μm	2 μm	4000	
Vein	0.5 cm	0.5 mm	40	54
Vena cave	3 cm	1.5 mm	18	

In systemic vessels there is an additional 12% in the heart and 18% in the pulmonary circulation.

Microcirculation

Microcirculation includes the precapillary sphincter region, capillaries and the smallest venules. The name (i.e. microcirculation) owes to its origin to the fact that they can be seen only under the microscope.

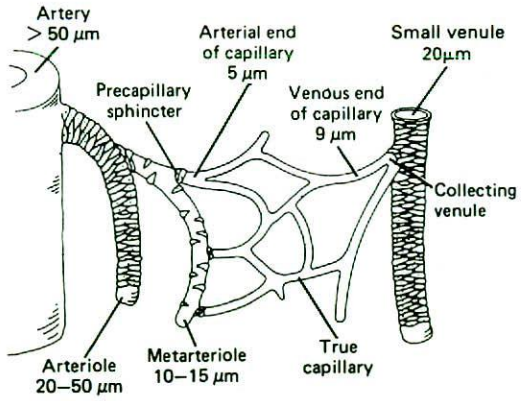


Fig. 6-13. *Microcirculation.*

Arterioles give rise to meta-arterioles which give rise to capillaries. The capillaries drain via a short collecting venules to the venules. The walls of the arteries, arterioles, and small venules contains relatively large amounts of smooth muscles. There are scattered smooth muscle cells in the walls of the meta-arterioles, and the opening of the capillaries are guarded by muscular preapillary spincters.

Factors affecting the caliber of the arterioles

Constriction	Dilation
Local factors	
Decreased local temperature	Increased CO_2 and decreased O_2
Autoregulation	Increased K^+,adenosine, lactate, etc.
	Decreased local pH
	Increased local temperature
Local hormones	No
Endothelin-1	Kinins
Locally released platelet serotonin	
Circulating hormones	
Epinephrine (except in skeletal muscle and liver	Epinephrine in skeletal muscle and liver
Norepinephrine	CGRP-alpha
AVP	Substance P
Angiotensin II	Histamine
Circulating Na^+- K^+ ATPase inhibitor	ANP
Neuropeptide Y	VIP
Neural factors	
Increased discharge of noradrenergic vasomotor nerves.	Decreased discharge of noradrenergic vasomotor nerves.
	Activation of cholinergic dilator fibers to skeletal. muscle

Circulation

Definition : It is the process of blood and lymph flow through a close system of vessels, called circulation.

Types of circulation

There are three types of blood circulation :

1. *Systemic circulation or greater circulation* : Passage of blood from left vetricle to the tissue and from the tissue to right atrium is called systemic circualation.
2. *Pulmonary or lesser circulation* : Passage of blood from right ventricle to the lungs & from the lungs to the left atrium is called pulmonary circulation.
3. *Portal circulation* : Blood from heart generally passes through one set of capillaries before draining into the heart. But in certain organ where the blood passes through two sets of capillaries or sinusoids before draining into the heart. The resulting system is known as portal system.

   It has two types :

   a. Arterial portal system e. g, renal circulation.
   b. Venous portal system e. g.
      i. Hepatic portal system.
      ii. Hypophyseal portal system.

Schemetic representation of the circulation of blood

Heart left ventricle	*Left atrium*
↓	↑
↓	**Pulmonary vein**
↓	↑
↓	Lungs
↓	↑
Large arteries	Pulmonary arteries
↓	↑
Medium arteries	Right ventricle
↓	↑
Small arteries	Right atrium
↓	↑
↓	Large veins
↓	↑

Arteries → ***Microcirculation*** → *Venules*

Importance of circulation

1. To supply the O_2, nutrition, vitamins to the tissue.
2. To carry away different metabolic waste product and CO_2 from tissue for elemination.
3. To prevent intravascular coagulation of blood.
4. Helps to maintain thermal balance through out the body.
5. Maintain optimum environment for cellular function.

Factors maintaining circulation

1. *Pumping action of heart :* This is the main motive force of circulation.
2. *Elastic recoil of arteries :* During ventricular systole certain amount of blood is being led directly into the aorta and thus vessel is stretched (Potential energy is gained). But due to elasticity of vessels wall and the aorta, recoils during ventricular diastole and thus blood moves forword (due to change of potential energy into kinetic energy for flow) towards the periphery.
3. *Pressure gradient :* Blood pressure gradually falls from the left to right side of heart, that is; in big arteries average pressure 120 mm of Hg, in the arterioles 50-60 mm of Hg, in the capillaries 15 mm of Hg and in the veins the pressure falls further, while the pressure near the heart is 0 mm of Hg. Due to this pressure gradient blood passes from higher to the lower pressure.
4. *Respiration :* During inspiration intra thoracic pressure falls and intra-abdominal pressure rises. Hence, with each inspiration, venous blood from abdomen is sucked up by the thorax, helps in venous return and acts as a great force in maintaining circulation.
5. *Muscular exercise :* When muscles contract, they squeeze the capillaries and veins, thus helps venous return and help in maintaining circulation.
6. *Effect of gravity :* Above the level of heart, it helps venous ruturn. but below the level of heart, it works aganist it.

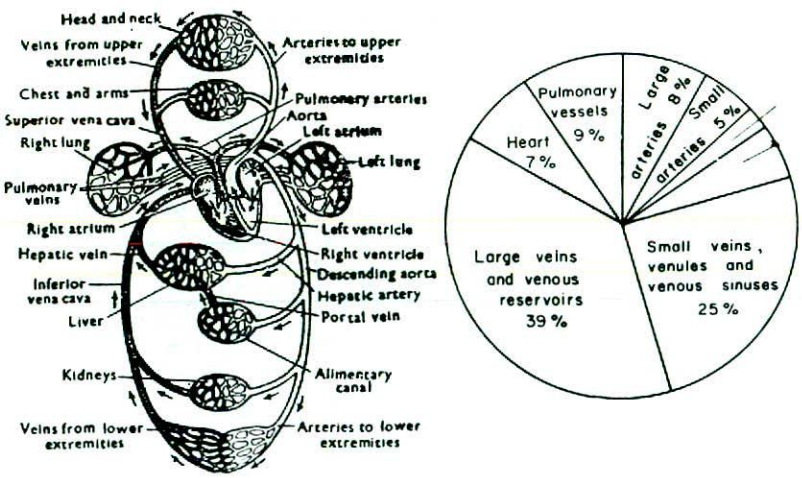


Fig. 6.14 *The different parts of circulatory system.*

Difference between systemic & pulmonary circulation

Systemic	*Pulmonary*
1. Passage of blood from left ventricle to tissues and from the tissues to right atrium.	1. Passage of blood from right ventricle to the lungs and from the lungs to the left atrium.
2. It begins in the left ventricle & via most of all part of body ends in the right atrium.	2. It begins in the right ventricle & via lungs ends in the left atrium.
3. Here artery carries oxygenated blood and veins carries deoxygenated blood.	3. Here pulmonary artery carries deoxygenated blood & pulmonary vein carries oxygendated blood.
4. It supplies nutrition to body tissue.	4. It carries blood to lungs for oxygenation.
5. Here BP is high.	5. Here BP is relatively low.

Q. 00. **What do you mean by high and low pressure system.**

i. High pressure system : The arterial system including the left ventricle.

ii. Low pressure system : The systemic veins, pulmonary circulation and heart chambers other than left ventricle. *(Ref. Ganong 21th Edition; page-589)*

Distribution of blood

Approximately 84 percent of the total blood volume of the body

is in the systemic circulation, with 64 % in the vein, 15 % in the arteries and 5 % in the capillaries. The heart contains 7 % of blood and the pulmonary vessels 9 %.

Q. 00. **State about the humoral regulation of circulation.**

Ans. *Humoral regulation of circulation* : Hormones regulate the circulation by constrict or dilate of the caliber of the arterioles :

i. *Hormones that constrict the arterioles* :
   a. *Local hormones* :
      1. Endothelin-1
      2. Locally released platelet serotonin
   b. *Circulating hormones* :
      1. Epinephrine (except in skeletal muscle and liver)
      2. Norepinephrine
      3. AVP
      4. Angiotensin II
      5. Circulating Na^+-K^+ ATPase inhibitor
      6. Neuropeptide Y.

ii. *Hormones that dilate the arterioles :*
   a. *Local hormones* :
      1. NO (nitrious oxide)
      2. Kinins
   b. *Circulating hormones* :
      1. Epinephrine in skeletal muscle and liver
      2. CGRP-alpha
      3. Substance P
      4. Histamine
      5. ANP
      6. VIP.

(Ref. Ganong 21th Edition; page-603)

(Q. Name the vasoactive substances affecting cardiovascular system.
Q. Name the factors affecting the caliber of the arterioles)

Q. 00. **Name the vasodilator and vasoconstirctor agents.**

Vasoconstrictor agent	*Vasodilator agent*
Local factors :	
Decreased local temperature	Increased CO_2 and decreased O_2
Autoregulation	Increased K^+,adenosine, lactate, etc.
	Decreased local pH
	Increased local temperature.
Endothelial products :	
Endothelin-1	NO
Locally released platelet serotonin	Kinins
Thromboxane A_2	Prostacycline
Circulating hormones :	
Epinephrine (except in skeletal muscle and liver)	Epinephrine in skeletal muscle and liver
Norepinephrine	CGRP-alpha
AVP	Substance P
Angiotensin II	Histamine
Circulating Na^+-K^+ ATPase inhibitor	ANP
Neuropeptide Y	VIP
Neural factors :	
Increased discharge of noradrenergic vasomotor nerves.	Decreased discharge of noradrenergic vasomotor nerves.
	Activation of cholinergic dilator fibers to skeletal muscle

(Ref. Ganong 22th Edition; page-603)

Blood Flow

Q. 00. ***Why blood flows through the vessels.***

Ans. Blood flows through the vessels because-

1. Forward motion imparted to it by the pumping of the heart.
2. Diastolic recoil of the walls of the arteries.
3. Compression of the veins by the skeletal mucles during exercise.
4. Negative pressure in the thorax during inspiration.

Resistance to flow depends on

1. Mostly upon the diameter of the vessels principally the arterioles.
2. Minor degree upon the viscosity of the blood.

Blood flow to the each tissue is regulated by :

1. Local chemical mechenisms.
2. General neural and hormonal mechenisms : That dilate or constrict the vessels of the tissue.

Biophysical consideration (*Arterial*)

i. ***Flow*** : In portion of the vascular system is equal to effective perfusion pressure in that portion divided by the resistance.

$$\text{Flow (F)} = \frac{\text{Pressure (p)}}{\text{Resistance (R)}}$$

ii. ***Effective perfusion pressure*** : It is the mean intraluminal pressure at the arterial end minus the mean pressure at the venous end.

iii. ***Velocity and flow of blood*** :
   1. Aorta (Proxiomal portion) : 40 cm/sec (Range : 120 - 0 cm/sec).
   2. Capillaries : About 0.07 cm/sec (Transient tissue from

the arteriole to the venular end of an average sized capillary is 1 - 2 seconds.)

3. Great veins : About : 10 cm/sec.

iv. ***Laminar flow*** : The flow of blood in the vesscls, like the flow of liquids in narrow rigid tubes, is normally laminar (Stream line).

1. Whithin the blood vessels, an infinitely thin layer of blood in contact with the wall of the vessel does not move.
2. The next layer within the vessels has a low velocity.
3. The next a higher velocity and so forth.
4. Velocity being greatest in the center of the stream.

Turbulence :

Laminar flow occurs at velocities up to a certain critical velocity. At or above this velocity, flow is turbulent. Turbulent flow creats sounds. The probability of turbulent is related to the-

i. Diameter of the vessels
ii. Viscosity of the blood.

$$Re =' \frac{PDV}{r}$$

Here, Re = Renolds number, named for the men who described the relationship.

P = Density of the fluid.

D = Diameter of the tube.

V› = Velocity of flow

n*= Viscosity of the fluid.

Interpretation :

1. Not turbulent : When Re is less than 2000
2. Turbulent : When Re is more then 3000.

Q. 00. **What is Reynold's number?**

Ans.

$$Re = \frac{PDV}{n}$$

Re = ***Renolds number***, named for the men who described the relationship.

P = Density of the fluid

D = Diameter of the tube

V = Velocity of flow

n*= Viscosity of the fluid.

Interpretation :

1. Not turbulent : When Re is less than 2000
2. Turbulent : When Re is more then 3000.

Viscosity :

1. Plasma : 1.8 times as viscus as water.
2. Whole blood : 3 - 4 times as viscus as water.

Thus viscosity depends most part on the hematocrit.

a. In polycythemia : viscosity increase.
b. In anaemia : viscosity decrease.
c. Condition (diseases) in which plasma protein /immunoglobins increase.
d. Diseases in which red blood cells are abnormaly rigid e.g hereditary spherocytosis.

Plasma Skimming

In the vessels, red cells tend to accumulate in the centre of the flowing stream. Consequently, the blood along the side of the vessels has a low hematocrit, and branches leaving a large vessel at right angles may receive a disproportionate amount of red -cell -poor blood. This phenomenon, which has been called plasma skimming.

Effect : Plasma skimming is the reason why the haematocrit of capillary blood is regularly about 25% lower than the whole body hematocrit.

Peripheral resistance

It is the resistance in which blood has to over come while passing through the periphery.

Factors affecting peripheral resistance :

Factors on which the peripheral resistance depends-

i. Velocity of blood
ii. Viscosity of Blood
iii. Elasticity of arterial walls
iv. State of lumen of blood vesesl.

Resistance in cardiovascular system is sometimes expressed in R units. Which are obtained by dividing pressure in mm Hg by flow in mL/Sec.

Example :

When the mean aortic pressure = 90 mm of Hg and left ventricular output = 90 mL/Sec.

Then,

$$\text{The total peripheral resistanc} = \frac{90 \text{ mm Hg}}{90 \text{ mL/Sec}}$$

$$= 1 \text{ R unit.}$$

Distribution of the circulating blood volume at rest :

1.	Systemic veins	: 50%
2.	Heart cavities	: 12%
3.	Pulmonary circulation	: 18%
4.	Aorta	: 2%
5.	Arteries	: 8%
6.	Arterioles	: 1%
7.	Capillaries	: 5%

(Blood in arteries = 16%)

When extra blood is administered by trunsfusion, less then 1% of it is distributed in the arterial system and all rest is

Region (Kg)	% of total CO	Blood flow		Consuption		Percentage of total O_2 consuption
		ml/min	*ml/100g/min*	*ml/min*	*ml/100g/min*	
1. Liver (2.6)	27.8	1500	57.7	51	2.0	20.4
2. Kidneys (0.3)	23.3	1260	420	18	6.0	7.2
3. Brain (1.4)	13.9	750	54	46	3.3	18.4
4. Skin (3.6)	8.6	462	12.8	12	0.3	4.8
5. Skeletal muscle (31)	15.6	840	2.7	50	0.2	20.0
6. Heart muscle (0.3)	4.7	250	84	29	9.7	11.6
7. Rest of the body (23.8)	6.2	336	1.4	44	0.2	17.6
Whole body (63)	*100*	*5400*	*8.6*	*250*	*0.4*	*100*

found in the systemic veins, pulmonery circulation and heart chambers other than the left ventricle.

*High pressure system : Arterial system +Lt ventricle.

*Low pressure system : all systemic veins, pulmonary circulation, heart chambers (right & left atrium +right ventricle).

Fluid exchange through the capillaries

(Equilibration with interstitial fluid) :

In capillary passages of substances are :

1. Substance passes through the junctions between endothelial cells and through fenestration (when they are present).
2. Some also pass through the cells by vesicular transport.
3. In case of lipid soluble substences, throguh the cytoplasm.

The factors other than vesicular transport that are responsible for transport across the capillary wall are -

a. Diffusion : e.g Nutrients, waste materials, O2, glucose, Co2 etc.

b. Filtration : Depends upon (across the capillary wall) :
   a. Hydrostatic pressure gradient
   b. Osmotic pressure gradient.

   (These two are also called starling forces.)

Fluid movement :

Thus, Fluid movement

$$= K[(P_c + p_i) - (P_i + p_c)]$$

Here,

K= Capillary filtration co-efficient (It takes into account and is proportionate to, the permeability of the capillary wall & the area available for filtration).

P_c= Capillary Hydrostatic pressure

P_i= Interstitial hydrostatic pressure. (It varies one organ to another, and there is considerable evidence that it is sub-atmospheric about (-) 2 mm Hg in subcutaneous tissue. It is positive in the liver and kidneys and is as high as 6 mm Hg in the brain.

p_c = Capillary colloid osmotic pressure

p_i = Interstitial colloid osmotic pressure.

p_i is usually negligible, so the osmotic pressure gradient (p_c - p_i) usually equals the oncotic pressure (i.e Capillary colliodal osmotic pressure).

So,

i. Fluid move into the interstitial space at the aroteriolar end of the capillary, where the filtration pressure across its wall exceeds the oncotic pressure.

ii. Fluid move into the capillary at the venular end, where the oncotic pressure exceeds the filtration pressure.

Filtration pressure :

a. Filtration pressure *(outward)* at the arteriolar end : (37-25) = 12 mm of Hg.

b. Filtration pressure (*inward*) at the venular end = (25-17) = 8 mm of Hg.

2. *In other capillaries* :
   i. Renal glomeruli : Fluid moves out of almost the entire length of the capillaries.
   ii. Intestines : Fluid moves into the capillaries through almost their entire length.

Total amount of filtration through the capillaries per day

= 24 Litre

1. This is about 0.3% of the cordiac out put.
2. About 85% of the filtered fluid is reabsorbed into the capillaries and the remainder returns to the circulation via the lymphatics.

Force causing reabsorption of fluid at the venous end of the capillary :

The low pressure at the venous end of the capillary changes the

balance of forces infavour of absorption as follows :

A. *Forces tending to move fluid inward :*
   i. Plasma colloidal osmotic pressure 28 mm Hg.
   Total inward force = 28 mm of Hg.

B. *Forces tending to move fluid outward :*
   i. Capillary pressure : 10 mm of Hg.
   ii. Negative interstitial free fluid pressure :(-) 3 mm of Hg (i.e outward force is 3 mm of Hg).
   iii. Interstital fluid colloid osmotic pressure : 8 mm Hg.

   Total outward force : 21 mm of Hg (10+3+8 = 21 mm Hg)

Summation of forces :

Inward force : 28 mm Hg.

Outward force : 21 mm Hg.

Net inward force = 7 mm of Hg.

Thus the force that causes fluid to move into the capillary, 28 mm of Hg, is greater than that opposing reabsorption, 21 mm Hg. The difference, 7 mm of Hg is the reabsorption pressure. This reabsorption pressure. (7 mm Hg) draws the fluid from the tissue space into the venous end of the capillary.

(Ref. Guyton & Hall11th Edition, Page 189)

Factors responsible for fluid exchange between the blood capillaries and intestitial space

The exchanges of fluid between plasma and the tissue spaces (interstitial spaces), both ways is a continuous process. The exchange has been considered to be due to the operation of the following factors :

1. *Capillary membrane and its permeability :*
   a. Lipid soluble materials through the cells
   b Lipid insoluble materials through the pores.
   c. Large molecular substances like protein dextran etc. through pinocytosis.
2. Diffusion
3. Filtration
4. Absorption
5. Metabolic activity of the tissue.

Forces causing filtration at the arterial end of the capillary

The approximate average forces operating at the arterial end of the capillary that cause movement through the capillary membrane are :

A. *Forces tending to move fluid outward :*
   1. Capillary hydrostatic pressure 30 mm of Hg.
   2. Negative interstitial free fluid pressure- 3mm Hg (i.e *Outward force 3 mm of Hg*).
   3. Interstitial fluid colloidal osmotic pressure- 8 mm Hg.

   Total outward force = 41 mm Hg(30+3+8 =41 mmHg).

B. *Forces tending to move fluid inward :*
   1. Plasma colloidal osmotic pressure- 28 mm Hg.
   Total inward force = 28 mm Hg.

Summation of forces :

Out ward forces : 41 mm Hg

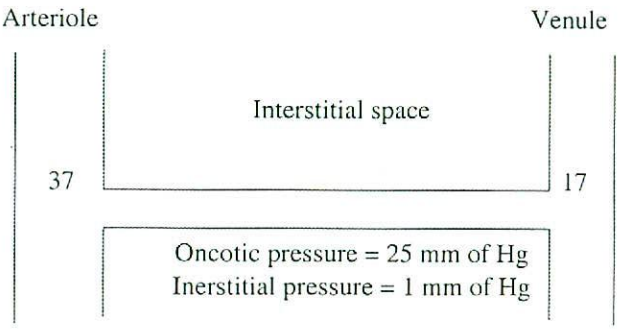
In ward forces : 28 mm Hg.

Net out ward force = 13 mm Hg (41-28 mm of Hg).

This 13 mm Hg filtration pressure causes on the average about 0.5 percent of the plasma to filter out of the arterial end of the capillaries into the interstitial spaces.

(Ref. Guyton & Hall-11th Edition, Page 189)

1. ***In Skeletal muscle :***



Lymphatic circulation

24 hours lymph flow = 2 - 4 litres.

Lymphatic vessels

1. *Initial lymphatics* (Lack of valve and smooth mucles in their wall) : They drain into the collceting lymphatics.
2. *Collecting lymphatics* (Have valves & smooth muscles in their walls).

Causes of flow :

a. Contraction of smooth mucles in peristaltic fashion (major factor).
b. Movement of skeletal muscles.
c. Negative intrathoracic pressure during inspiration.
d. Suction effect of high velocity flow of blood in the veins in which the lymphatics terminates.

Functions :

1. Fluid efflux normally exceeds influx across the capillary walls, but the extra fluids enters the lymphatics and drain through them back into the blood.
2. Proteins are returned to the blood stream via lymphatics (is equal to 25-50% of total circulating plasma protein /day) mainly from liver & intestine and smaller quantities from other tissues.

3. The transport of absorbed long chain fatty acids & cholesterol from the intestine via the lymphatics.

Capillary circulation :

At any one time, only 5% of the circulating blood is in the capillaries, but this 5% is in a sense the most important part of the blood volume because it is across the systemic capillary walls that O_2 and nutrients enter the interstitial fluid and Co_2 and waste products enter the blood stream. The exchange across the capillary walls is essential to the survival of the tissues.

Lymphatic circulation

Fluid efflux normally exceeds influx across the capillary walls, but the extra fluid enters the lymphatics and drains through them back into the blood. This keeps the intestinal fluid pressure from rising and promotes the turnover of the tissue fluid . The normal 24 hours lymph flow is 2 - 4 litre.

Functional anatomy :The lymphatic channels are present in every tissue, excepting the central nervous system and cornea. The lymph channels start as blind capillaries lined by single layer of endothelium but no basement membrane. In these blind capillaries tissue fluid and some protein molecules enter from the tissue. But these fluid and protein molecules, once they enter these channels, cannot leave them. These vessels then drain into bigger vessels which are fewer in number, which in turn, open into still bigger (and still fewer in number) vessels. Ultimately all lymphatic fluid opens into right and left subclavian veins respectively. Thus the fluid and the protein of the tissue fluid are returned to the blood.

On its way the lymphatic channels are interrupted by lymph nodes. On approaching a lymph node, a lymph channel breaks up into several afferent channels, all of which enter the lymph nodes. From the lymph node one (or sometimes more) single channel, called efferent channel, draining the lymph node, emerges and continues onward. The lymph node adds lymphocytes and antibodies to the flowing lymph. Therefore, these lymphocytes and antibodies eventually enter the blood in the subclavian vein. The lymphatic channels contain valves which ensure a unidirectional flow.

Functions of the lymph :

1. Plasma proteins which somehow excape into the tissue fluid are returned by the lymph flow. It has been calculated that about 200 gms of protein are returned to the blood through the lymphatics per day. In addition, the lymphatic circulation also carries hormones to some extent.
2. The lymphocytes and the antibodies enter the blood via the lymph.
3. The lymph nodes destroy any incoming bacteria. Thus if there be a bacterial infection, the afferent channels contain bacteria, but as the bacteria enter the lymph node, they are destroyed, so the efferent channel is sterile (bacteria free). Before entering blood, the lymph thus passes through about eight lymph nodes.
4. From the intestine, big lipid molecules (plus a little proteins) enter the lymph channels within the villi and thus enter the blood. Such big fatty molecules are called chylomicrons. After a heavy fat meal, the serum is often milky because of heavy concentration of chylomicron in it.

Interstitial fluid volume :

Interstitial fluid volume = 15% of total body weight (or 75% of extracelluar fluid component).

Interstitial fluid depends upon :

1. Capillary pressure
2. Interstitial fluid pressure
3. The oncotic pressure
4. The capillary filtration co-efficient
5. The numbers of the active capillaries
6. The lymph flow
7. The total ECF volume : The ratio of pre-capillary to post-capillary venular resistance is also important.

N.B.
Edema : is the accomulation of interstitial fluid in abnormally large amount.

Causes of increase interstitial fluid volume and edema :

1. Increased filtration pressure :
   a. Arteriolar dilatation
   b. Venular constriction
   c. Increased venous pressure
      i. Heart failure
      ii. Incompetent valve
      iii. Venous obstruction
      iv. Increased total ECF volume
      v. Effect of gravity etc.
2. Decreased osmotic pressure gradient across the capillary :
   a. Decreased plasma protein level.
   b. Accumulation of osmotically active substances in interstitial space
3. Increased capillary permeability
   a. Substance P
   b. Histamine & related substance
   c. Kinins, etc.
4. Inadequate lymph flow.

(Ref. Ganong 22th Edition)

Cerebral Circulation

a. Vessels :
   1. Two internal carotid arteries.

2. Two vertebral arteries.

The vertebral arteries unite to from the basilar artery and the basilar artery and the carotids form the circle of Willis below the hypothalamus.

The circle of Willis is the orgin of the six large vessels supplying the cerebral cortex.

N.B. A relatively small fraction of the total arterial flow is carried by the vertbral orteries.

There is no crossing over, probably because the pressure is equal on both sides i.e one carotid artery is distributed almost exclusively to the cerebral hemisphere on that side.

b. ***Anastomoses*** : There are precapillary anastomoses between the cerebral arterioles but flow through these channels is generally insufficient to maintain the circulation and prevent infarction when a cerebral artery is occluded.

c. ***Venous drainage*** :

1. Deep veins
2. Dural sinuses.

These veins empties principally into internal jagular veins. Although a small amount of blood drains through the ophthalmic & pterygoid plexus -through emissary veins to the scalp and down the system of paravertebral veins in the spinal canal.

d. ***Anatomical features of brain capillaries*** :

1. *Non fenestrated.*
2. *There are tight junctions between the endothelial cells* : That limits the passages of substances through the junctions.
3. *There are relatively few vesicles in the endothelial cytoplasm* : So there is little vesicular transport (i.e endocytocytosis & exocytosis).
4. *The brain capillaries are surrounded by the end feet of astrocytes* : These endfeet are closely applied to the basal lamina of the capillaries, but they do not cover the entire capillary wall and there are gaps of about 20 nm between endfeet. However the endfeet induce the tight junctions in the capillaries.

e. ***Nerve Innervation*** :

3 Systems of nerve innervate the crebral blood vessels :

1. Postganglinic sympathetic neurons.
2. Cholenergic neuron.
3. Postganglionic cholenergic neuron.

Q. 04. ***Name the factors that regulate cerebral circulation.**

Ans. *Factors affecting overall cerebral blod flow are:*

i. Intracranial pressure
ii. Local constriction and dilation of cerebral arteries.
iii. Mean arterial pressure at brain level
iv. Viscosity of blood
v. Mean venous pressure at brain level.

(Ref. Ganong 22th Edition; page-617)

Coronary circulation

The right atrium receives blood through the superior venacava (blood is collected from upper part of body), the inferior venacava (blood from lower part of body), the coronary sinus and other smaller veins draining the wall of heart (venae cordis minimie and anterior cardiac vein).

From right atrium blood passes into right ventricle through right atrio-ventricular opening. From right atrium blood passes into the lungs through pulmonary trunk.

The left atrium receives the blood from the lungs through four pulmonary veins. The blood from left atrium passes into the left ventricle via left atrioventricular orifice.

From the left ventricle blood enters into the ascending aorta via aortic opening and passes into systemic circulation.

Q. 05. ***Give clinical importance of coronary circulation.**

Ans. When flow through a coronary artery is reduced to the point that the myocardium it supplies becomes hypoxic, 'P factor' accumulates and ***angina pectories*** develops. If the myocardial ischemia is severe and prolonged, irreversible changes occur in the muscle, and the result is ***myocardial infarction***. The most common cause of myocardial infraction is rupture of an atheroslerotic plaque, or hemorrhage into it, which triggers the formation of a coronary occluding clot at the site of the plaque.

(Ref. Ganong 22th Edition; page 622)

Q. 01. ***Name the factors that regulate coronary circulation.**

Ans. *Variations in coronary flow* : At rest, the heart extracts 70-80% of the O_2 from each unit of blood delivered to it. O_2 consumption can be increased significantly only by increasing blood flow. Therefore, it is not surprising that blood flow increases when the metabolism of the myocardium is increased. The caliber of the coronary vessels, and consequently the rate of coronary blood flow, is influenced not only by pressure changes in the aorta but also by chemical and neural factors. The coronary circulation shows considerable autoregulation.

i. ***Chemical factors*** : The close relationship between coronary blood flow and myocardial O_2 consumption indicates that one or more of the products of metabolism cause coronary vasodilation. Factors suspected of playing this role include O_2 lack and increased local concentrations of CO_2, H^+, K^+, lactate, prostaglandins, adenine nucleotides, and adenosine. More than one of these vasodilator metabolites could be involved. Asphyxia, hypoxia, and intracoronary injections of cyanide all increase coronary blood flow 200-300% in denervated as well as intact hearts, and the feature common to these three stimuli is hypoxia of the myocardial fibers. A

similar increase in flow is produced in the area supplied by a coronary artery if the artery is occluded and then released. This ***reactive hyperemia*** is similar to that seen in the skin. There is evidence that in the heart it is due to release of adenosine. The adenosine appears in addition to ameliorate the reperfusion-induced injury that occurs when blood flow is reestablished.

(Ref. Ganong 22th Edition; page 622)

ii. ***Neural factor*** : The coronary arteries contain a- adrenergic receptors, which mediate vasoconstriction, and b- adrenergic receptors, which mediate vasodilatation.

(Ref. Ganong 22th Edition; page 622)

Pulmonary circulation

1. ***Vascular bed*** : Pulmonary vascular bed resembles the systemic circulation except -
   i. Thickness : Walls of the pulmonary artery and its large branches are about 30% as thick as the wall of the aorta and small arterial vessels.
   ii. Arterioles : are endothelial tubes with relatively little muscle in their walls.
   iii. Post capillary vessel wall : There is also some smooth pulmonary capillaries : are large, and there are multiple anastomoses, so each alveolus sits in a capillary of basket.
2. ***Pressure*** : The entire vascular system is a distensible low pressure system.
   i. Systolic blood pressure : 24 mm of Hg.
   i. Diastolic blood pressure : 9 mm of Hg.
   ii. Mean pressure : 15mm of Hg.
   iii. Blood pressure in left atrium: 8 mm of Hg

   So pressure gradient = 15 - 8 mm of Hg = 7 mm of Hg.

   N.B. Pressure fall from the pulmonary artey to the capillaries is relatively small.

   Capillary blood pressure =10 mm of Hg (about).
3. ***Volume*** :

   At any one time is about 1 litre.

   In capillaries less than 100 ml.
4. ***Velocity*** : Root of the pulmonary artery : 40 cm/sec (about) (as that in aorta).

   It falls of rapidly then rises slightly again in the larger pulmonary veins.

   A red cell gets time to traverse the pulmonary capillaries-
   a. At rest : 0.75 second
   b. During exercise : 0.3 second or less.
5. ***Eflect of gravity on blood flow*** :

   There is linear increase in pulmonary blood flow from the apices to the bases of the lungs.
   1. The pressure in the capillaries at the top of the lungs : is close to the atmospheric pressure in the alveoli and is just sufficient to maintain perfusion.
   2. In the middle portion of the lungs : The pulmonary arterial and capillary pressure exceeds alveolar pressure.
   3. In the lower portion of the lungs : Alveolar pressure is lower than the pressure in all parts of the pulmonary circulation and blood flow is determined by the arterial-venous pressure difference.

   N.B For details of pulmonary pressure, pl follow the *Respiratory system.*

Peripheral pooling of blood

Results when an individual rises from a supine to an erect position. Standing causes approximately 500 ml of blood to shift from the pulmonary circulation to the dependent veins of the legs. In the absence of reflex compensations, there is a reduction in venous return.

Venous circulation

Blood flows through the blood vessels, including the veins primarily because of the pumping action of the heart, although venous flow is aided by the heart beat, the increase in the negative intrathoracic pressure during each inspiration, and contractions of skeletal muscles that compress the veins (muscle pump).

Venous Pressure & Flow : The pressure in the venules is 12-18 mm Hg. It falls steadily in the larger veins to about 5.5 mm Hg in the great veins outside the thorax. The pressure in the great veins all their entrance into the right atrium (Cental venous pressure) averages 4.6 mm Hg but fluctuates with respiration and heart action.

Peripheral venous pressure, like arterial pressure, is affected by gravity. It is increased by 0.77 mm Hg for each cm below the right atrium and decreased by a like amount for each 1cm above the right atrium the pressure is measured.

When blood flows from the venules to the large veins, its average velocity increases as the total cross sectional area of the vessels decreases. In the great veins, the velocity of blood is about one-fourth that in the aorta, averaging about 10 cm/second.

Circulation through the special regions

Resting blood flow & O_2 consumption of various organs in a 63 kg adult man with a mean arterial blood pressure of 90 mm of Hg and an O_2 consumption of 250 ml/min.

Blood Pressure

Arterial pressure :

1. In the aorta and in the brachial and other large arteries : 120/70 mm of Hg.

a. Mean pressure = About 50 mm of Hg.

2. In the large & medium sized arteries : pressure falls slightly, because their resistance to flow is low.
3. In the small arteries & arterioles : Pressure falls rapidly, because these are the main sites of peripheral resistance.
   a. Mean pressure at the end of the arterioles = 30 - 35 mm of Hg.
   b. Pulse pressure at the end of the arterioles = 5 (about) mm of Hg.

Gravitational effect : The pressure in any vessel above the heart level is decreased and that in any vessel, below the heart lvel, increased- is about 0.77 mm Hg/cm.

Example : If pressure at heart level = 100 mm of Hg

i. 50 cm above the heart, the pressure is- 62 mm of Hg (100-0.77x50 = 100-38.5 = 61.5 mm of Hg).
ii. 105 cm below the heart level the pressure is- 180 mm of Hg (100 + 0.77x105 = 100 + 80 = 180 mm of Hg).

Capillary pressure : Capillary pressure vary considerably. Typical values in human nail bed capillaries are-

1. At the arteriolar end : 32 mm of Hg.
2. At the venous end : 15 mm of Hg.

Pulse pressure :

1. At the arteriolar end : about 5 mm of Hg.
2. At the venous end : approximately (0) mm of Hg.

Venous pressure :

1. In the venules : 12 -18 mm of Hg.
2. Larger veins : 5.5 mm of Hg. (about)
3. Cetral venous pressure : 4.6 mm of Hg. But flactuates with respiration & heart action.

   (Cetral pressure is the pressure of the great veins at their entrance into the right atrium).

   Gravitational effect : It increased by 0.77 mm Hg for each cm below the right atrium and also decreased by 0.77 mm of Hg for each cm above the right atrium.
4. The mean pressure at the anticubitul vein = 7.1 mm of Hg.

Shock

Q. 00. ***What is shock?**

i. *Defination :* It is an abnormal physiological condition resulting from inadequate propultion of blood to the aorta thus causes inadequate blood flow perfusing the capillaries of tissues and organs.

ii. *Types of shocks* :
   1. Hypovolumic shock :
      a. Haemorrhagic
      b. Traumatic
      c. Dehydration
      d. Burn
   2. Cardiogenic shock
      a. Myocardial infarction
      b. Congestive cardiac failure
      c. Arrythmias
   3. Normovolemic shock (septic shock, anaphylatic shock)
   4. Neurogenic shock.

   (Q. *Classify shock. *or* name the types of shock.).

Tissue necrosis in severe shock

Not all cells of the body are equally damaged by shock because some tissues have better blood supplies than others. For instance, the cells adjacent to the arterial ends of capillaries receive better nutrition than the cells adjacent to the venous ends of the same capillaries. Therefore, one would expect more nutritive deficiency around the venous ends of capillaries than elsewhere. For instance necrosis in the center of a liver lobule, the portion of the lobule that is last to be bathed by the blood as it passes through the liver sinusoids.

Similar punctate lesions occur in heart muscle, although here a definite repetitive pattern, such as occurs in the liver, cannot be demonstrated. Nevertheless, the cardiac lesions play an important role in leading to the final irreversible stage of shock. Deteriorative lesions also occur in the kidneys, especially in the epithelium of the kidney tubules, leading to kidney failure and occasionally uremic death several days later. Deterioration of the lungs also often leads to respiratory distress and death several days later- called the shock lung syndrome.

(Ref. Guyton& Hall-11th Edition; page 283)

Hemorrhage

It means abnormal internal or external discharge of blood. It may be arterial, venous or capillary. Arterial blood is bright red; flows in spouts. Capillary blood is of a reddish colour; exudes fom tissue. Venous blood is dark red; flow is continuous.

Q. 03. ***What are the compensatory haemodynamic responses that occur to maintain adequate tissue blood flow following acute moderate haemorrhage.**

Ans. *Compensatory reactions activated by hemorrhage*:

i. Vasoconstriction
ii. Tachycardia
iii. Venoconstriction
iv. Tachypnea → increased thoracic pumping
v. Restlessness → increased skeletal muscle pump- ing (in some cases)
vi. Increased movement of interstitial fluid into capillaries
vii. Increased secretion of norepinephrine and epinephrine
viii. Increased secretion of vasopressin
ix. Increased secretion of glucocorticoids
x. Increased secretion of renin and aldosterone

xi. Increased secretion of erythropoietin
xii. Increased plasma protein synthesis.

(Ref. Ganong 22th Edition; Page 637)

Q. 00. **State the effect of-**

i. potassium	v. acetylcholine
ii. calcium	vi. atropine
iii. sodium	vii. temperature

iv. adrenaline - on heart function.

i. *Effect of potassium (K^+) on heart :*

a. *Excess potassium* in the extracellular fluids causes the heart to become extremely dilated, and flaccid and slows the heart rate.

b. *Very large quantities* can also block conduction of the cardiac impulse from the atria to the ventricles through the AV bundle. Elevation of potassium concentration to only 9 to 12 mEq/ liter-two to three times the normal value can cause such weakness of the heart and abnormal rhythm that this can cause cardiac death.

(Ref Guyton & Hall-11th Edition; page 113)

ii. *Effect of calcium (Ca^{++}) on heart* :

a. An excess of calcium ions causing the heart to go into spastic contraction opposite to effect of K^+. This is due to direct effect of Ca^{++} ion in exciting the cardiac contractile process.

b. Conversely, a deficiency of Ca^{++} causes cardiac flaccidity, similar to effect of K^+.

(Ref Guyton & Hall-11th Edition; page 113)

iii. *Effect of sodium (Na^+) on heart* :

a. An excess of sodium ions depresses the cardiac function, that is dilate and flaccid the heart and slows the heart rate as that of K^+ but for an entirely different reason.
Na compete with Ca^{++}, i.e the greater the sodium ion concentration in the extracellular fluid the less the effectiveness of the Ca^{++} in causing contraction when an action potential occurs.

(Ref Guyton & Hall-11th Edition)

iv. *Effects of adrenaline* : It increases the rate and force of contraction. It-
i. Stimulates SA and AV node
ii. Increases conductivity and automaticity.

v. *Effect of acetylcholine* : It decreases the rate and force of contraction of heart.

vi. *Effect of atropine* : At low dose it lowers the heart rate by vagul stimulation. But at high dose it increases heart rate by medullary stimulation.

vii. *Effect of temperature* : Increase body temparature, increases heart rate by directly stimulating the SA node.

Concept of hydrostatic pressure and oncotic pressure

Hydrostatic pressure

Hydrostatic pressure is the pressure which is caused by the effects of gravity on a fluid filled system *i.e* it occurs as a result of the weight of the blood in the vessels.

Types with normal values : :
i. Capillary hydrostatic pressure (Pc) range : 30-45 mm Hg
ii. Interstitial hydrostatic pressure (Pi) range : 1 mm Hg.

Effects :
i. *Capillary hydrostatic pressure* : An increase in capillary hydrostatic pressure results in increase in filtration (i.e. outward flow).
ii. *Interstitial hydrostatic pressure* : An increase in interstitial hydrostatic pressure hinders additional fluid filtration from the capillaries.

Oncotic pressure

Oncotic pressure results from the osmotic pressure of blood proteins.

Types with normal values :
i. Plasma colloid osmotic pressure : 25-27 mm of Hg
ii. Interstitial oncotic pressure : 5-10 mm of Hg.

Importance / significance :
i. *Plasma colloid osmotic pressure* (blood oncotic pressure) provides a force that tends to reabsorb fluid into the capillaries from the interstitial space.
ii. *Interstitial oncotic pressure* tends to pull fluid out the vascular system.

Vascular endothelium

The walls of the blood vessels are made up of a single layer of endothelial cells. Endothelium occupies a strategic interface between blood and body. The endothelial lining varies from organ to organ.

Types of endothelium :
i. *Continuous type of endothelium* : The junctions between endothelial cells permit the passage of molecules up to 10 mm in diameter. They are found in vascular beds of skeletal, cardiac and smooth muscle.
ii. *Fenestrated endothelium* : Large transcellular openings (2000-20,000 nm) exist in the endothelial cells. They are found in most endocrine glands. GIT and parts of the kidney (renal glomeruli).
iii. *Endothelium with tight junctions* : Junctions between endothelial cells are lighter (fused), though physiological evidence suggestive of presence of pores approximately 400 nm in diameter. They are found in most body tissue and brain (no pores).

iv. *Endothelium with gap junctions* : There is large gap between endothelial cells, so endothelium is extremely porous and discontinuous. They are found in vascular bed of bone marrow, liver, and spleen i.e. in sinusoidal capillaries.

Functions of endothelium : The vascular endothelium is a *cardiovascular endocrine organ*. It is an active metabolic tissue and has many regulatory rules :

i. *Vasomotor control* : Enzyme located on the endothelial surface control the level of circulatory compounds such as bradykinin, serotonin, angiotensin and adenine nucleotides.

ii. *Maintenance of an adequate organ blood flow* : Endothelial derived substance *endothelial derived relaxing factor (EDRF)* or *nitric oxide (NO)* evokes relaxation of vascular smooth muscle and have anti-platelet property.

iii. *Pro and anti-thrombotic mechanism* : The normal endothelium is negatively charged (platelet also negatively charge) anti-thrombotic surface, which under physiological conditions does not react with platelets or blood constituents. The endothelial lining of the blood vessels also forms prostacycline that inhibits platelet aggregation.

iv. *Metabolic and immunological functions* :

v. *Regulation of vascular cell growth*

vi. *Modulation of imunoresponses*.

Substances secreted by the endothelium

Endothelial cells synthesize a number of mediators which contribute to the physiological control of circulation, vascular tone, and platelets functions.

These include :

i. *Prostacycline ($PG\text{-}I_2$)* : Prostacycline is synthesized by endothelial cells from arachidonic acid via cyclo-oxygenase pathway. Endothelial cells can produce cyclo-oxygenase enzyme also. Prostacycline promotes vasodilatation and inhibits platelets aggregation i.e. counteracts to thromboxane A_2.

ii. *Endothelial derived relaxing factor (EDRF) or NO* : The endothelial derived relaxing factor (EDRF), has now been identified as nitric oxide (NO). NO is synthesized from arginine by the enzyme *NO synthase*. The release of NO can be triggered by the sheer stress (flow) and by a number of substances including bradykinin, histamine, noradrenaline, substance P, platelet products, serotonin, and thrombin.

iii. *Endothelins (ET_5)* : Endothlein are the families of 21 amino acid polypeptide produced by the endothelial cells. At least three different types of endothelins are recognized.
   a. Endothelin-1 (ET-1) : Brain, kidney and endothelial cells.
   b. Endothelin-2 (ET-2) : Intestine.
   c. Endothelin-3 (ET-3) : Intestine and adrenal glands.

Functions of endothelins :

1. *Cardiovascular effects* :
   a. Long lasting vasoconstriction followed after initial vasodilatation.
   b. Positive chronotropic and ionotropic effects on myocardium.
2. *Neuroendocrine effects* :
   a. Increase plasma level of ANP, renin, aldosterone and catecholamines.
   b. Modulates synaptic transmission.
3. *Gastrointestinal tract* : Regulates gastrointestinal blood flow.
4. *Metabolism* : Enhances gluconeogenesis
5. *Renal effects* :
   a. Renal vasoconstriction, decrease GFR, and renal blood flow
   b. Decrease Na^+ reabsorption through inhibition of Na^+-K^+ ATPase.
6. *Pulmonary effects* : Causes bronchoconstriction.

Hypertension

The level of blood pressure varies with age, sex, race and country. Hypertension is defined arbitrarily at levels above generally accepted *normals*, for example 140/90 mm Hg at the age of 20, 160/95 mm Hg at the age of 50.

WHO criteria includes :

160/95 : definitely hypertensive

140/90 : borderline hypertensive.

Classification of hypertension

Classification	*Range (mm Hg)*
i. ***Diastolic*** :	
a. Normal	: < 85
b. High normal	: 85-89
c. Mild hypertension	: 90-104
d. Moderate hypertension	: 105-114
e. Severe hypertension	: > 115
ii. ***Systolic (when diastolic <90)*** :	
a. Normal	: < 140
b. Borderline systolic hypertension	: 140-159
c. Isolated systolic hypertension	: > 160

Clinical classification : Clinically hypertension is classified as-

i. *Primary or essential hypertension (90-95%)* : In the large majority cases no cause can be identified, and this form of hypertension is know as primary or essential hypertension.

ii. *Secondary hepertension (10%)* : A cause of hypertension can be discovered in less than 10% of patients; such are known as secondary hypertension.

Causes of hypertension

i. *Essential or primary hypertension* : No single factor has been found; many factors are probably responsible :
   a. Genetic and familial
   b. Socio-economic : related to social deprivation
   c. Dietary factors : obesity, high salt intake, high alcohol
   d. Humoral factors : high renin, reduced NO, ANP
   c. Neurotransmitter : acetylcholine, noradrenaline, substance P, serotonin, dopamine.

ii. *Secondary hypertension* :
   a. Renal diseases : Glomerulonephritis, pyelonephritis, polycystic kidney disease.
   b. Endocrine causes : Pheochromocytoma, Cushing syndrome, acromegaly.
   c. Cardiovascular causes : Coarctation of aorta.
   d. Drugs : Estrogen containing oral contraceptives, anabolic steroids, vasopressin etc.

Features of hypertension

i. May be asymptomatic

ii. Patient may present with complications due to hypertension:
   a. Congestive cardiac failure
   b. Hypertensive encephalopathy
   c. Cerebral hemorrhage or infraction (stoke)
   d. Hypertensive retinopathy
   c. Progressive renal failure.

3. Occasionally headache.

Circulation 6.56 *Cardiac cycle 6.64* *Heart rate 6.69* *Heart sound 6.70* *Blood presure 6.71*
Cardiac muscle 6.60 *Cardiac output 6.66* *Pulse 6.70* *ECG 6.71* *Applied 6.76*

***Direction** : Write T for true & F for false against each of the following statement.*

Circulation

Q. 01. **In physiological state**
- T a. capillaries contain 5% blood.
- F b. veins contain 25% blood.
- F c. arterioles contain 10% blood.
- F d. veins contain 5% blood.
- F e. capillaries contain 25% blood.

Q. 02. **Veins differ from the arteries in that**
- T a. they are considered as capacitance vessels
- T b. they show more distensibility.
- T c. their tunica media have lesser quantity of smooth muscles.
- F d. they have more hydrostatic pressure.
- F e. they offer more resistance to blood flow.

Q. 03. **Arterioles**
- T a. provide most of the peripheral resistance.
- T b. play a major role in the regulation of blood pressure
- T c. play a major role in the regulation of local blood flow.
- F d. are known as exchange vessels.
- F e. play a major role in the regulation of heart rate

Q. 04. **Systemic veins**
- T a. contain valves that pmmote venous return during muscular activity.
- T b. act as a capacitance vessels in the circulation.
- T c. constrict in response to sympathetic activation.
- F d. are the main resistance vessels in the circulation.
- F e. have a lower compliance than systemic arteries.

Q. 05. **Vein**
- T a. is made of thin vascular wall.
- T b. contains most of the blood.
- T c. has sympathetic vasoconstrictor innervations.
- F d. receives nutntion from vasa vasornm arising from their lumen.
- F e. is known as resistance vessel.

Q. 06. **The venous system can act as a reservoir for peripheral blood chiefly because of the**
- T a. large volume capacity of the venous system
- F b. low oxygen saturation in the venous system
- F c. low compliance of the venous wall.
- F d. absence of smooth muscle fibers in the venous wall.
- F e. superficial location of the veins.

Q. 07. **Blood flow**
- T a. may be increased locally by endothelial production of nitric oxide.
- T b. is inversely proportional to vascular resistance.
- F c. to the heart is maximum during ventricular systole.
- F d. to the skin is largely under local metabolic control.
- F e. to the brain is largely under autonomic nervous control.

Q. 08. **The blood flow**
- T a. is inversely proportional viscosity of the blood.
- T b. increases when blood volume is increased
- T c. is directly proportional to the vessel diameter
- F d. is directly proportional to viscosity of the blood
- F e. decreases when blood volume is increased

Q. 09. **Blood flow (Velocity) is**
- T a. increased if resistance is decreased.
- T b. inversely proportional to the hematocrit value.
- F c. inversely proportional to the cross sectional area of vessel.
- F d. the greatest in the aorta.
- F e. not a major determinant of blood pressure.

Q. 10. **The velocity of the blood flow is**
- T a. lower in the vein than in the arteries.
- T b. higher in the arteries than in the arterioles.
- F c. higher in the venules than in the arterioles.
- F d. higher in the capillaries than in the arterioles.
- F e. higher in the vein than in the arteries.

Q. 11. **Least change of blood flow during exercise occur in**
- T a. brain.
- F b. intestine.
- F c. heart.
- F d. skin.
- F e. kidney.

Q. 12. **During exercise blood flow**
- T a. remains same in abdominal organs.
- T b. decreases in skin.
- T c. increases in active muscle.

F d. decreases in lungs and heart.
F e. increases in skin.

Q. 12. **Circulatory adjustment occurs during exercise by**
T a. increasing the cardiac output.
T b. increasing the sympathetic activity over heart.
T c. increasing the arterial pressure.
F d. decreasing the total peripheral resistance.
F e. decreasing the myocardial force of contraction

Q. 13. **Positive ionotropic agents**
T a. are mediated by β-adrenergic receptors.
T b. decrease left ventricular end-diastolic pressure.
F c. decrease the ventricular performance.
F d. are mediated by muscarinic receptors.
F e. decrease maximum left ventricular pressure.

Q. 14. **With increasing distance from the heart, arterial**
T a. PO_2 falls.
T b. walls contain more smooth muscle than elastic tissue.
F c. flow has a greater tendency to be turbulent.
F d. walls contain less smooth muscle than elastic tissue.
F e. mean pressure tends to rise slightly.

Q. 15. **Net outward force in the foot will be increased by**
T a. fall in plasma colloid osmotic pressure.
T b. decreased plasma albumin concentration.
T c. increased cpaillary permeability.
F d. increased interstitial fluid pressure.
F e. arteiolar constriction.

Q. 16. **Vasovagal fainting or syncope**
T a. is associated with skeletal muscle vasodilation
T b. is more likely to occur in standing than lying position.
T c. is loss of consciousness.
F d. is associated with tachycardia.
F e. is more likely to occur in a cold than hot environment.

Q. 17. **Increased sympathetic drive to the heart**
T a. increases the rate of conduction in purkinje fiber.
T b. increases the rate of impulse generation.
T c. increases the myocardial metabolis
F d. decreases the ejection fraction of the left ventricle.
F e. decreases the coronary blood flow.

Q. 18. **Sympathetic drive to the heart is increased**
T a. in excitement.
T b. in exercise
T c. in hypotension.
F d. during sleep.
F e. when parasympathetic drive is decreased.

Q. 19. **Vasoconstriction occurs due to**
T a. norepinerphrine secretion.
T b. formation of angiotensin II.
T c. increased K^+
T d. release of thromboxane A_2
F e. release of CO_2

Q. 20. **Peripheral resistance increases due to**
T a. dehydration.
T b. vasoconstriction.
T c. increased viscosity of blood.
F d. increased distance of a blood vessel from the heart.
F e. anemia.

Q. 21. **Resistance to blood flow is**
T a. the lowest in capillary.
T b. inversely proportional to diameter.
T c. directly proportional to haematocrit.
F d. directly proportional to diameter.
F e. determined by arterial pressure.

Q. 22. **Distribution of vascular resistance**
T a. Small arteries & arterioles : 47 %
T b. Capillaries : 27 %
T c. Arteries : 19 %
T d. Veins : 7 %.
F e. None

Q. 23. **Maximum oxygen content in fetus is in**
T a. umbilical vein.
F b. pulmonary vein.
F c. thoracic inferior vena cava.
F d. ductus arteriosus.
F e. descending aorta

Q. 24. **Maximum resistance to blood flow occurs in the**
T a. meta-arterioles.
T b. arterioles.
F c. capillaries.
F d. aorta.
F e. vena cava.

Q. 25. **Local metabolic activity is the chief factor for determination the rate of blood flow to**
T a. skeletal muscle.
T b. heart.
F c. kidney.
F d. skin.
F e. lung.

Q. 26. **Coronary blood flow increases during**
T a. stimulation of parasympathetic nerve.
T b. myocardial hypoxia
T c. adenosine infusion
F d. early systole
F e. stimulation of parasympathetic nerve

Q. 27. **Coronary blood flow is increased by**
T a. β-adrenergic blockadge.

F b. a decrease in systemic blood pressure.
F c. vagal stimulation.
F d. a decrease in arterial PO_2
F e. an increase in arterial PCO_2

Q. 28. **Myocardial blood flow to the left ventricles increases during**
T a. stimulation of sympathetic nerves to the heart.
T b. myocardial hypoxia.
T c. adenosine infusions.
F d. arterial hypertension.
F e. early systole.

Q. 29. **Coronary artery blood flow**
T a. is regulated mainly by myocardial O_2 consumption.
T b. accounts for about 5% of the cardiac output.
F c. does not depend upon arterial blood pressure.
F d. is greatest during systole in the left coronary artery.
F e. is greatest during diastole in the right coronary artery.

Q. 30. **Coronary blood flow is**
T a. regulated by autonomic nervous system.
T b. decreased in the reflex response to a fall in the arterial blood pressure.
T c. more during diastole than systole.
F d. stable throughout the cardiac cycle.
F e. is increased during early systole.

Q. 31. **Coronary blood flow increases during**
T a. adenosine infusion
T b. hypertension
T c. myocardial hypoxia
F d. decreased myocardial activity
F e. ventricular systole.

Q. 32. **Forces tending to move fluid outwards across the capillaries are**
T a. negative interstitial free fluid pressure.
T b. interstitial fluid colloid osmotic pressure.
T c. capillary hydorstatic pressure at arterial end.
F d. plasma colloid osmotic pressure.
F e. capillary hydrostatic pressure at venous end.

Q. 33. **Lymph is formed**
T a. 2 -3 liters/ day.
T b. from interstital fluid.
F c. 0.5 -1 liter/day.
F d. from venous blood.
F e. from capillary fluid.

Q.34. **Effects of excess potassium ion in ECF on heart are**
T a. heart may be flaccid.
T b. A-V conduction block may occur.
T c. heart become extremely dilated.
F d. heart rate will be increased.
F e. heart may be spastic.

Q. 35. **Coronary vasodilators released during ischemia of cardiac muscle are**
T a. hydrogen ion.
T b. adenosine.
T c. potassium ion.
F d. bicarbonate ion.
F e. sodium ion.

Q. 36. **Anginal pain due to coronary artery disease**
T a. may be elicited by sudden exposure to cold.
T b. is typically made worse by treatment which lowers the systemic blood pressure.
T c. may be precipitated by anaemia.
F d. is caused by accumulation of metabolites in the myocardium.
F e. is relieved by sympathomymetic drugs.

Q. 37. **Pulmonary circulation differs from systemic circulation in that it**
T a. consists of vessels of larger diameter
T b. is mixed with systemic circulation in the heart
T c. low resistance circuit
F d. consists of thick walled vessels
F e. is considered as greater circulation.

Q. 38. **CapIllaries with tight junctions allowing the passage of only small molecukes are found in**
T a. Brain
F b. Skin
F c. Kidney
F d. Muscle
F e. None.

Q. 39. **Hypoxia causes vasoconstriction in**
T a. Lungs
F b. Muscle
F c. Liver
F d. Spleen
F e. All.

Q. 40. **Blood flow through a vessel varies directly with**
T a. Pressure difference
F b. Resistance
F c. Viscosity
F d. Length of vessel.
F e. None

Q. 41. **Hypovolemic shock is characterised by the following**
T a. Hypotension
T b. Cold and clammy skin
T c. Intense thirst
T d. Tachycardia
F e. Inhibition of respiration

Q. 42. **Maximum surface area is present in**
- T a. Capillary
- F b. Arterioles
- F c. Artery
- F d. Vein.
- F e. All.

Q. 43. **Most permeable capillaries**
- T c. Kidney
- F a. Post pituitary
- F b. Liver
- F d. Small intestine
- F e. Lung

Q. 44. **Pre capillary sphincter relaxation is caused by**
- T a. Local metabolites
- F b. Circulating catecholamines
- F c. Sympathetic activity
- F d. Fall in capillary pressure
- F e. Viscosity.

Q. 45. **Which one of the following is the correct sequence in increasing order of their basal blood supply (ml/min/100 gm of tissue)?**
- T a. Brain, heart, kidney
- F b. Heart, brain, kidney
- F c. Brain, kidney, heart
- F d. Kidney, heart, brain
- F e. All.

Q. 46. **Blood brain barrier is deficient at**
- T a. Area postrema
- F b. Thalamus
- F c. Meta thalamus
- F d. Cerebellum
- F e. Pons.

Q. 47. **The regional arterial resistance of the mesenrty and kidney vessels is reduced by**
- T a. Dopamine
- F b. Dobutamine
- F c. Nor adrenaline
- F d. Isoprenaline
- F e. Leukotrine.

Q. 48. **Adrenaline increases all of the following in heart except**
- T a. Refractory period
- F b. Automaticity
- F c. Conduction velocity
- F d. Contractility
- F e. All.

Q. 49. **Increased blood flow in muscle during exercise is not because of**
- T a. High lactate
- F b. Low pH
- F c. High CO_2
- F d. Low PO_2
- F b. All.

Q. 50. **Splanchnic circulation in vigrous activity is affected by**
- T a. Decrease capacitance with shunting of blood
- F b. Decrease blood supply due to vasoconstriction
- F c. Decrease blood supply due to venoconstriction
- F d. Increase capillary congestion
- F e. All.

Q. 51. **The followings tend to increase in old aget**
- T a. Residual volume
- T b. Systolic BP
- T c. Pulse pressure
- F d. Vital capacity
- F e. All.

Q. 52. **During exercise, blood flow does not decrease in**
- T a. Coronary circulation
- F b. Cutaneous circulation
- F c. Hepatosplanchnic circulation
- F d. Renal circulation.
- F e. Intestinal circulation.

Q. 53. **Blood brain barrier is maximum permeable to**
- T a. CO_2
- F b. Na^+
- F c. K
- F d. Chloride
- F e. Ca.

Q. 54. **Blood brain barrier is made up of**
- T a. Astrocytes
- F b. Oligodendrocytes
- F c. Oligodendroglia
- F d. Microglia
- F e. Macroglia.

Q. 55. **Coronary blood flow stops during**
- T a. Isovolumetric contraction
- F b. Protodiastole
- F c. End of diastole
- F d. Isometric contraction
- F e. Ejection phase.

Q. 56. **Splanchnic vesels and venules contain what perocen tage of blood volume:**
- T a. 20 - 30%
- F b. 10 - 20%
- F c. 40 - 50%
- F d. 60 - 70%
- F e. 12 - 13%

Q. 57. **All of the following ions cause vasodilatation**
- T a. Kinins
- T b. Mg
- T c. K
- F d. Ca
- F e. None

Q. 58. **Major blood reservoirs of the body include the following**
- T a. Liver sinuses
- T b. Major abdominal veins
- T c. Venous plexus of the skin
- T d. Venous sinuses of the spleen
- F e. Throracic vena cava

Q. 59. **Velocity of blood is times that of urine:**
- T a. 5-6 times more that of water
- F b. Same as of ECF
- F c. 10 times of urine
- F d. 5-6 times less that of water
- F e. 3 times more that of water

Q. 60. **Velocity of blood flow is inversely proportional to:**
- T a. Cross-sectional area
- F b. Viscosity
- F c. Flow
- F d. Length
- F e. None

Q. 61. **Turbulant blood flow is produced by**
- T a. Decreased harmatocrit
- F b. Decreased velocity of circulation
- F c. Decreased cardiac output
- F d. All of the above
- F e. None of the above

Q. 62. **Select the statement which best characterises lymph capillaries**
- T a. Have a discontinuous basement membrane
- F b. Have smaller diameter than blood capillaries
- F c. Less permeable than blood capillaries
- F d. Have no endothelial lining
- F e. All.

Q. 63. **What one structural feature do all blood capillaries have in common?**
- T a. A continuous basement membrane
- F b. Absence of intracellular fenestrations in the endothelial cells
- F c. Presence of intracellular fenestrations
- F d. A discontinuous basement membrane
- F e. Remain patent in the healthy subject

Q. 64. **Venoconstriction is exhibited by**
- T a. Carotid artery occlusion
- T b. Valsalva manoeuvre
- T c. Asphyxia
- T d. Haemorrhage
- F e. Lying down.

Q. 65. **What does prevent blood loss after rupture of small blood vessel?**
- T a. Vasuconstriction
- T b. Formation of fibrin threads
- T c. Formation of platelet plug
- T d. Production of haematoma to increase pervascular pressure
- T e. All.

Q. 66. **Vascular distensibility is least for the following vascular segment**
- T a. Systemic artery
- F b. Pulmonary artery
- F c. Systemic vein
- F d. Pulmonary vein
- F e. All.

Q. 67. **Blood flow through left coronary artery**
- T a. Increases when myocardial hypoxia is present
- F b. Regulated by sympathetic vasedilator nerves
- F c. Creates during early systole
- F d. Decreased in reflex response to fall in blood pressure
- F e. None.

Q. 68. **What best characterises the sinusoids?**
- T a. Are not found in skeletal muscle
- F b. Have smaller diameter than lymph capillaries
- F c. Have a continuous endothelial lining
- F d. Have a continuous besement membrane
- F e. None.

Q. 69. **Sympathetic vasoconstrictor tone is diminished in response to increased activity of**
- T a. Carotid sinus pressor receptors
- F b. Carotid body chemoreceptors
- F c. Pain receptors
- F d. Medullary chemoreoeptors
- F e. None.

Q. 70. **Maximum surface area of circulating system is seen in**
- T a. Capillaries
- F b. Arteries
- F c. Veins
- F d. Arterioles
- F e. Vena cava.

Cardiac muscle

Q. 71. **Cardiac muscles**
- T a. have more myoglobin than that of skeletal muscle

T b. have intercalated disc
T c. are inteitonnected as latticework fashion
F d. have many tight junctions
F e. act as single syncytium.

Q. 72. **Cardiac muscle is characterized by having**
T a. the same graphic relation between initial fiber length total tension as skeletal muscle.
T b. a T system located at the Z lines.
T c. intercalated disks connecting muscle fibers.
F d. same action potential as that of skeletal muscle
F e. the same refractoiy period characterstics of skeletal muscle.

Q. 73. **Intercalated disks are found in**
T a. cardiac muscle
F b. skeletal muscle
F c. nervous tissue
F d. smooth muscle
F e. glandular tissue.

Q. 74. **Properties of cardiac muscle are**
T a. refractory period.
T b. conductivity.
T c. autoexcitability.
F d. adaptation.
F e. summation.

Q. 75. **Impulse generating power of junctional tissues are**
T a. purkinje fibres : 15-40 impulses/min.
T b. SA node : 70-80 impulses/min.
F c. A-V node : 30-36 impulses/min.
F d. bundle of His : 15-40 impulses/min.
F e. inter nodal pathway : 20-40 impulses /min.

Q. 76. **The cardiac impulse is**
T a. transmitted through the S-A node at a velocity of 0.05 m/second
T b. transmitted from S-A node within 0.03 seconds.
F c. generated in atrioventricular (A-V) node
F d. transmitted from right atrium to left atrium through inter nodal pathways
F e. rapidly transmitted through atrioventricular (A-V) bundle.

Q. 77. **Sinoatrial node cells are**
T a. innervated by the vagus
F b. unable to generate impulse when completely denervated.
F c. found in both atria
F d. connected to the AV node by fine bundles of purkinje tissue.
F e. stable with regard to their membrane potentials

Q. 78. **Conduction velocity in the SA node is**
T a. 0.05 meter/second
F b. 0.5 meter/second
F c. 0.4 meter/second
F d. 1 meter/second
F e. 4 meter/second

Q.79. **Sino-atrial node cells are**
T a. innervated by the vagus nerves
F b. connected to the A-V node by fine bundles of purkinje
F c. called reserve pace-maker
F d. found in both atria
F e. unable to generate impulses when heart is completely denervated.

Q.80. **SA nodal fibers**
T a. transmit impulses at a higher velocity.
T b. are inherently leaky to sodium ions.
F c. have threshold voltage of about -55 mV.
F d. need external impulse for their stimulation.
F e. originate impulse at a rate of 100 beats/min normally.

Q. 81. **SA node**
T a. is the normal pace marker of heart.
T b. is innervated by vagus.
T c. discharges most rapidly.
T d. controls the beat of the heart.
F e. has contractile element.

Q. 82. **The sinoatrial node is normally the pacemaker of the heart because**
T a. it initiates the cardiac impulse.
T b. of its highest rate of impulse generation.
F c. it is controlled by autonomic nervous system
F d. it is located in the right atrium.
F e. of its proximity to AV node.

Q. 83. **Pacemaker potential of SA node**
T a. results from decreasing K^+ conductance.
T b. depends upon increasing Ca^{++} conductance.
F c. slows with hyperkalemia.
F d. spreads up in vagus stimulation.
F e. results from decreasing Na^+ conductance.

Q. 84. **Prominent pacemaker is seen in**
T a. sinoatrial node.
F b. bundle of His.
F c. purkinje fibers.
F d. atrial muscle cells.
F e. ventricular muscle cells.

Q. 85. **Which of the following normally has the most promi nent pre potential?**
T a. SA node
F b. purkinje fibers
F c. ventricular muscle cell.

F d. artial muscle cell
F e. bundle of His

Q. 86. **A-V nodal delay occurs as**
T a. very few gap junctions between the fibers.
T b. the fibres are smaller than atrial muscle fibers.
T c. resting membrane potentials are much less negative.
F d. A-V node recieves the impulse originating from S.A node
F e. it acts as a reserve pacemaker.

Q. 87. **AV nodal delay**
T a. is shortened by sympathetic stimulation.
T b. is due to diminished number of gap junctions in conducting pathway.
T c. is about o.16 second.
T d. enhances ventricular filling.
F e. is due to excess calcium.

Q. 88. **The Purkinje tissue cells in the heart**
T a. are responsible for the short duration of QRS complex.
T b. are responsible for the configuration of the QRS complex.
T c. conduct impulses faster than some neurous.
T d. are larger than ventricular myocardial cells.
F e. lead to contraction of the base before the apex of the heart.

Q.89. **Purkinje fibers**
T a. have very few myofibrils
T b. transmit cardiac impulse at the highest rate
F c. are thin
F d. contain few amount of glycoprotein
F e. contain less number of gap junctions.

Q. 90. **Increased sympathetic drive to the heart**
T a. increases the rate of conduction in purkinje fiber.
T b. increases the rate of impulse generation.
T c. increases the myocardial metabolis
F d. decreases the ejection fraction of the left ventricle.
F e. decreases the coronary blood flow.

Q. 91. **The portion of the heart with the fast conduction velocity for action potential is the**
T a. purkinje fibers.
F b. Left atrium
F c. bundle of His
F d. Right atrium
F e. the ventricles

Q. 92. **Cardiac impulse are produced due to the opening of**
T a. L Channel of calcium.
T b. slow calcium-sodium channel.
T c. T Channel of calcium.
T d. K Channel.
F e. fast sodium channel.

Q. 93. **Conduction of the wave of depolarization in the heart is slowest in the**
T a. A-V junctional tissue.
F b. atrium.
F c. venticular endocardium.
F d. ventricle.
F e. purkinje fibers.

Q. 94. **The last part of the heart to be depolarized are**
T a. uppermost portion of the septum.
T b. posterobasal portion of the left ventricle.
T c. pulmonary conus.
F d. posterior part of the right atrium.
F e. interatrial septum.

Q. 95. **Ventricular muscle receives impulses directly from the**
T a. purkinje system.
F b. AV node.
F c. bundle of His.
F d. right and left bundle branches.
F e. SA Node.

Q. 96. **Plateau is present in the action potential of**
T a. cardiac muscle.
F b. skeletal muscle.
F c. smooth muscle.
F d. nervous tissue.
F e. connective tissue.

Q. 97. **Plateau in the cardiac muscle**
T a. is due to slow calcium-sodium channel.
T b. causes muscle contruction to last up to 15 times as long as in skeletal muscle.
F c. is due to fast sodium channel.
F d. is due to efflux of K^+
F e. is due to efflux of Na^+.

Q.98. **Contractility of myocardium can be increased by**
T a. moderate increase of body temperature
T b. infusion of fluid containing calcium
T c. increased stimulation of sympathetic nerves
F d. increased stimulation of baroreeeptors
F e. infusion of potassium containing fluid.

Q. 99. **Repolarization phase of action potential of ventri cular muscle fibers is caused by the opening of**
T a. K^+ Channels.
F b. HCO_3 channels.
F c. Na^+ Channels.
F d. Cl^- Channels.
F e. Ca^{++} channels.

Q. 100. **Cardiac glycosides (digitalis) enhances the contrac tile process of cardiac muscle fibers by**
- T a. inhibiting the Na^+-K^+ATP ase of cell membrane
- F b. stimulating cardiac β-adrenergic receptors.
- F c. blocking cardiac β-adrenergic receptors.
- F d. stimulating intracellular production of cAMP.
- F e. decreasing the amount Ca^{++} available to myofibrils.

Q. 101. **Due to Frank-Starling mechanism of heart**
- T a. both the heart rate and force of contraction is increased
- T b. within physiological limit, heart pumps all the blood that comes to it
- T c. their is no damming of blood in peripheral circulatory system
- F d. heart muscle can not be tetanized
- F e. atria can complete its contraction before the contrac tion of the ventricle

Q. 102. **Myocardial contractility is increased by**
- T a. increasing the interaction force between actin and myosin filaments
- T b. increasing the initial length of cardiac muscle within physiological limit
- T c. local application of acetylcholine
- F d. local application of epinephrine
- F e. decreased sympathetic activity.

Q. 103. **Force of contraction of heart**
- T a. is increasesd in aneima
- F b. is not related to nutrition
- F c. is decreasesd by increased ventricular filling
- F d. is increased with parasympathetic stimulation
- F e. is decreased by athletic training.

Q. 104. **Force of contraction of heart muscle depends upon**
- T a. circulatory hormones.
- T b. sympathetic stimulation.
- T c. Ca^{++} level in ECF.
- T d. initial length of muscle fibers.
- F e. parasympathetic stimulation.

Q. 105. **The strength of contraction of verticular muscle**
- T a. is more when peripheral resistance is increased.
- T b. is more during strenuous exercise.
- T c. increases when end diastolic venticular filling pressure rises.
- F d. increases when serum potassium level rises.
- F e. increases when blood calcium level falls.

Q. 106. **Increased vagal tone leads to**
- T a. decreased AVconduction
- F b. increased heart rate.
- F c. increased refractrory period of atria
- F d. increased ventricular contractility
- F e. increased ectopic beats

Q. 107. **Conduction velocity is least in**
- T a. AV node
- F b. Bundle of HIS
- F c. SA node
- F d. Purkinjee fibres
- F e. All.

Q. 108. **Fastest conducting tissue in human heart**
- T a. Purkinje fibres.
- F b. AV node
- F c. SA node
- F d. Bundle of His
- F e. None.

Q. 109. **Velocity of transmissions is fastest through following part of heart.**
- T a. Bundle of His
- F b. AV node
- F c. Atria
- F d. Ventricle
- F e. Internodal pathway

Q. 110. **Adrenaline increases the following in heart**
- T a. Contractility
- T b. Automaticity
- T c. Conduction velocity
- F d. Refractory period
- F e. All.

Q. 111. **Parasympathetic stimulation would decrease the following**
- T a. Atrial
- T b. SA node rhythmicity contractility
- T c. Heart rate
- F d. A-V conduction time
- F e. All.

Q. 112. **Absolute refractory period in heart**
- T a. Lasts till cardiac contraction
- T b. Longer than refractory period in skeletal muscle
- T c. A phase of cardiac cycle in which heart cannot be stimulated by any amount of stimulus
- T d. Corresponds with duration of action potentiai
- T e. All of the above

Q. 113. **Right and left vagus respectively go to :**
- T a. SA node, AV node
- F b. AV node, SA node
- F c. AV node, bundle of His
- F d. SA node, bundle of His
- F e. All.

Q. 114. **Repolarization of ventricular muscle**
- T a. Begins in apical epicardium
- F b. Occurs last at apex
- F c. Begins in septum

F d. Begins at AV node
F e. Begins at SA node.

Q. 115. **For cardiac muscle, V max can be used as a measure of**
T a. Rhythmicity
F b. Excitability
F c. Contractility
F d. Conductivity
F e. All.

Q. 116. **A decrease in the velocity of impulse conduction through the A-V node will usually cause**
T a. The P0 interveal to increase
F b. The P0 interval to decrease
F c. Disappearance of the T-wave
F d. Increased heart rate
F e. Atrial fibrillation

Q. 117. **Fibres of A-V junction**
T a. Modified muscle fibres
F b. Modified nerve fibres
F c. Highly contractile
F d. Conduct impulse rapidly
F e. All.

Q. 118. **Aortic valve incompetence characteristically produce**
T a. Hypertrophied left ventricle
T b. Increased myocardial blood flow
T c. Increased pulse pressure
T d. All of the above
F e. None.

Q. 119. **Absolute refractory period of heart is the gap of time in which**
T a. No action potential from another part of heart will reexcite the heart muscle
F b. Heart is in diastole
F c. Unresponsive to neural stimuli
F d. None of the above
F e. All.

Q. 120. **When pacemaker is in another area of heart, it denotes**
F a. Abnormal conducting tissue
F b. Abnormal S-A node
F c. Abnormal with neural controlling system
F d. All of the above
T e. None of the above

Q. 121. **In wolff parkinson white syndrome, there exists a connection between atria and**
T a. Ventricles
F b. Bundle of His
F c. AV node
F d. Purkinjee fibres
F e. None of the above

Q. 122. **SA Node**
T a. Initiates the impulse at faster rate
F b. Generate the impulse spontaneously
F c. Increases the parasympathetic activity
F d. Increases sympathetic activity
F e. None of the above

Q. 123. **Vagal stimulation can cause**
T a. Delayed A-V conduction
T b. Increased ventricular contraction
T c. Decreased heart rate
F d. Increased atrial contraction
F e. All.

Q. 124. **Myocardial oxygen demand**
T a. Directly proportional to Heart rate
F b. Inversely proportional to heart rate
F c. Increased by digitalis
F d. Not related to heart rate
F e. All.

Q. 125. **Vagus inhibits pacemaker potential by**
T a. Hyperpolarisation
T b. Increased pre potential
T c. Increase k^+ permeability
F d. Stabilising resting membrane potential
F e. All.

Q. 126. **Conduction velocity is maximum in**
T a. Bundle of His
F b. SA node
F c. AV node
F d. Right ventricle
F e. Atria.

Q. 127. **SA node is located**
T a. Subepicardially
F b. Epicardially
F c. Intramyocardial
F d. Endocardially
F e. None.

Cardiac cycle

Q. 128. **Cardiac cycle**
T a. time is inversely proportional to heart rate.
T b. is composed of systole and diastole.
T c. beings with the atrial systole.
F d. begins with the ventricular systole.
F e. time is directly proportional to heart rate.

Q. 129. **During cardiac cycle**
T a. the contracting ventricles shorten from apex to base

T b. the atrioventricular (A-V) valves close at the beginning of systole
F c. systole begins in the left atrium
F d. first heart sound is heard in protodiastole
F e. atrial and ventricular systole occur simultaneously.

Q. 130. **During cardiac cycle**
T a. the cyclical changes are same in each beat of the heart.
T b. contraction begins normally in the right atrium.
F c. impulses spread directly from atria to ventricle.
F d. sometimes 4th heart sound can be auscultated.
F e. murmurs are produced normally.

Q. 131. **Cardiac cycle time is**
T a. inversely proportional to the heart rate.
T b. affected mostly in diastole.
F c. affected mostly in systole.
F d. eight seconds.
F e. directly proportional to the heart rate.

Q. 132. **During isometric contraction phase of ventricle**
T a. both the atrio-ventricular and semilunar valves are closed.
T b. there is production of QRS complex.
T c. intraventricular pressure sharply rises.
F d. there is production of 3rd heart sound.
F e. the pressure in the aorta is rising.

Q. 133. **Regarding isovolumic (isometric) contraction period of ventricular systole**
T a. it continues until the ventricular pressure overcome the pressure in the aorta and the pulmonary artery.
T b. ventricles contract as a closed cavity.
T c. ventricular contraction occurs but there is no emptying of blood.
F d. shortening of the length of the ventricular muscles occurs.
F e. volume of the ventricular contents decrease

Q. 134. **In isovolumetric ventricular contraction phase of the cardiac cycle**
T a. atrial pressure decreases.
T b. ventricular pressure increases rapidly.
F c. there is opening of A-V valves.
F d. there is an increased atrial pressure.
F e. there is rapid rise of aortic pressure.

Q. 135. **During isometric ventricular contraction period**
T a. no change of ventricular blood volume occurs.
T b. both the atrioventricular and semilunar valves are closed.
T c. there is sharp rise of ventricular pressure
F d. the atrioventricular valves are open and semilunar valves are closed.
F e. there is sharp rise of atrial pressure

Q. 136. **In isometric contraction period**
T a. the duration is 0.05 second.
T b. ventricles are in systole.
T c. ventricles are contracting as closed cavities.
F d. there is a shortening of cardiac muscle.
F e. semilunar valves remain open.

Q. 137. **During rapid ejection phase of ventricular systole**
T a. aortic pressure is rising.
T b. mitral valve is closed.
F c. ventricle will be expelled to its minimal volume.
F d. aortic valve is closed.
F e. first heart sound is produced.

Q. 138. **During protodiastolic period there is**
T a. porduction of 2nd heart sound.
F b. closure of semilunar valve.
F c. opening of A-V valve.
F d. isometric relaxation of ventricle.
F e. isotonic contraction of ventricle.

Q. 139. **During ventricular diastole, ventricular filling**
T a. gives rise to third heart sound in children
T b. gives a concept of preload.
T c. is most rapid in the first half of diastole.
F d. is occured about 80% by atrial contraction.
F e. begins during isometric relaxation of ventricle.

Q. 140. **Ventricular filling**
T a. (25%) occurs due to atrial contraction.
T b. causes 2nd and 3rd heart sounds.
T c. occurs due to rapid rush of blood from atria
F d. occurs due to blood coming from inferior vena cava.
F e. causes production of 1st heart sounds.

Q. 141. **Ventricular filling**
T a. depends on filling time.
T b. depends on atrial contraction.
T c. begins during isovolumetric relaxation period
F d. begins during isovolumetric contraction period
F e. can occur only when artial pressure is greater than atmospheric pressure.

Q. 142. **Immediately after closure of semilunar valves, there is**
T a. isotonic relaxation
T b. isometric relaxation phase
F c. isotonic contraction
F d. isometric contraction phase
F e. production of 1st heart sound.

Q. 143. **In isometeric relaxation period**
T a. both the valves remain closed.

T b. ventricles are relaxing as closed cavities.
F c. the blood enters into the ventricle from atria
F d. intraventricular pressure rises.
F e. duration is 0.05 second.

Q. 144. **Semilunar valves open**
T a. when ventricular pressure rises above aortic pressure.
T b. when ventricular pressure rises above 80 mmHg.
F c. when ventricular pressure rises above 120 mmHg.
F d. when atrial pressure rises above ventricular pressure.
F e. when atrial pressure rises above ventricular pressure.

Q. 145. **Cardiac cycle duration in man is**
T a. 0.8 seconds
F b. 0.4 seconds
F c. 1.2 seconds
F d. 1.6 seconds
F e. 8.0 seconds

Q. 146. **What is true for extrasystole in ventricle?**
T a. Fails to produce radial pulse
T c. Associated with abnormal QRS complex
T d. Tendency to be followed by a compensatory pause
F b. Hints at serious heart ailment
F e. All.

Q. 147. **Ventricular filling**
T a. Produces 3rd heart sound in some healthy persons
F b. Depends mainly on contraction of atria
F c. Begins during isometric ventricular relaxation
F d. Will not occur unless atrial pressure is higher than atmospheric pressure
F e. All.

Q. 148. **Which of the following is true about ventricular filling**
T a. Filling pressure is important for cardiac output
F b. Atrial contraction mainly contributes
F c. Maximum during isometric ventricular relaxation
F d. Lnotropic state of myocardium limits the cardiac output.
F e. None.

Q. 149. **The cause of post extrasystolic potentiation is**
T a. Ca^{++}
F b. K^{+}
F c. Na^{+}
F d. Mg^{++}
F e. Cl^{-}.

Cardiac Output

Q. 150. **The cardiac output**
T a. is increased when storke volume is increased
T b. from the right and left ventircle are the same
T c. raises in hot environment.
F d. is not increased when heart rate is increased
F e. usualy rises when a person stands up.

Q. 151. **Cardiac output**
T a. increases when stroke volume rises.
T b. is greater than cardiac index.
T c. usually rises when a person lies down.
F d. does not rise after exercise.
F e. does not depend on venous return.

Q. 152. **Factors regulating cardiac out put are**
T a. heart rate.
T b. peripheral resistance.
T c. venous return.
F d. exercise.
F e. posture.

Q. 153. **Factors affecting cardiac output are**
T a. end diastolic volume (EDV)
T b. heart rate.
T c. storke volume.
F d. total peripheral resistant (TPR)
F e. end systolic volume (ESV)

Q. 154. **Cardiac output is increased by**
T a. increasing heart rate in response to exercise
T b. increasing ventricular end-diastolic volume
T c. increased β-sympathetic nervous system activity.
F d. the administration of digoxin to normal subjects at rest.
F e. increasing ventricular after-load.

Q. 155. **Cardiac output is not affected by**
T a. sleep
F b. pregnancy
F c. high environmental temperature.
F d. exercise
F e. anxiety

Q. 156. **Fick's principle is used for measuring**
T a. Cardiac output
F b. GFR.
F c. Blood pressure
F d. Pulse pressure
F e. Lung volumes

Q. 157. **Cardiac output in liter per minute divided by heart rate is the index**
T a. mean stroke volume.
F b. mean arterial pressure.
F c. cardiac index.
F d. ejection fraction.
F e. cardiac efficiency.

Q. 158. **Organ to have the maximum oxygen consumption after liver is**
- T a. skeletal muscle
- F b. heart
- F c. kidney
- F d. brain
- F e. skin.

Q.159. **Cardiac output increases**
- T a. in lying posture
- F b. with increased heart rate of about 200 beats/minute
- F c. during expiration
- F d. with stimulation of baroreceptors
- F e. with increased systolic pressure

Q. 160. **Cardiac output**
- T a. usually rises when a person lies down.
- T b. rises in hot environment.
- T c. is normally expressed as the output of one ventricle in liters/minutes.
- T d. may not increase when heart rate rises.
- F e. does not increase in exercise following denervation of the heart.

Q. 161. **Ejection fraction of the heart**
- T a. is the portion of end diastolic volume that is ejected by heart.
- T b. is the guideline for conraction of heart.
- F c. is reduced in exercise.
- F d. is normally 10%.
- F e. is increased during sleep.

Q. 162. **Venous return depends upon**
- T a. mean systemic filling pressure.
- T b. pressure defference between capillaries and venules.
- T c. muscular exercise.
- T d. respiration.
- F e. resistance to blood flow.

Q. 163. **Factors affecting venous return are**
- T a. pumping action of heart.
- T b. gravity.
- T c. muscle activity.
- F d. arterial blood pressure.
- F e. heart rate.

Q. 164. **Within physiological limit, increased venous return**
- T a. increases force of contraction of heart.
- T b. increases cardiac output.
- F c. decreases systolic blood pressure.
- F d. decreases intrathoracie pressure.
- F e. decreases heart rate.

Q. 165. **Venous return is enhanced during exercise by**
- T a. decreasing cardiac output.
- T b. venoconstriction.
- T c. skeletal muscle pump.
- T d. increased depth of inspiration.
- F e. decreased blood volume.

Q. 166. **End diastolic volume depends on**
- T a. filling time.
- T b. filling pressure.
- T c. cardiac distensibility.
- T d. artial contraction.
- F e. myocardial contraction.

Q. 167. **If the end diastolic volume increases**
- T a. starling's law is applicable
- T b. stroke volume is increased.
- F c. cardiac output is decreased.
- F d. the force of contraction of heart decreases.
- F e. heart rate is decreased.

Q. 168. **A decrease in storke volume results from**
- T a. decrease in ventricular compliance.
- T b. decrease in ventricular contractility.
- F c. decrease in ventricular afterload.
- F d. decrease in heart rate.
- F e. increase in ventricular preload.

Q. 169. **In the denervated heart, left venticular storke work increases when**
- T a. right ventricular output increases.
- T b. the veins constrict.
- T c. the end diastolic length of the ventircular fibers increases.
- T d. peripheral resistance rises.
- F e. blood volume falls.

Q. 170. **During exercise**
- T a. heart rate is increased
- T b. sympathetic discharge increases
- T c. venous return increases
- F d. O_2 uptake by the exercising muscle decreases
- F e. total peripheral resistance increases

Q. 171. **Which of the following organ extracts the greatest amount of O_2 from the blood that it receives?**
- T a. lung.
- T b. heart.
- F c. skin.
- F d. kidney.
- F e. brain.

Q. 172. **When vasoconstrictor discharge is increased there is**
- T a. increased cardiac output
- T b. decreased blood stores in the venous reservoirs.
- T c. increased arteriotar constriction
- T d. increased blood pressure
- F e. decreased heart rate

Q. 173. **Preload of the heart is determined by**
- T a. End diastolic volume
- F b. Ejection systolic volume
- F c. End systolic volume
- F d. Systolic vascular resistance
- F e. Peripheral resistance.

Q. 174. **Normal hepatic blood flow per minute is**
- T a. 50 cc/100 gm of liver tissue
- F b. 100 cc/100 gm of liver tissue
- F c. 200 cc/100 gm of liver tissue
- F d. 300 cc/100 gm of liver tissue
- F e. 150 cc/100 gm of liver tissue

Q. 175. **Ejection fraction increases with**
- T a. End. diastolic volume
- F b. End systolic volume
- F c. Peripheral vascular resistance
- F d. Venodilation
- F e. None.

Q. 176. **Ejection fraction of the ventricle refers to the ratio of**
- T a. Stroke volume / end diastolic volume
- F b. Amount of blood received / amount of blood ejected
- F c. End-systolic volume / end diastolic volume
- F d. Stroke volume / end systolic volume.
- F e. None.

Q. 177. **Direct Fick method of measuring cardiac output requires estimation of :**
- T a. O_2 content of arterial blood
- T b. O_2 consumption per unit time
- T c. Arteriovenous O_2 difference
- T d. O_2 content of blood from right ventricle
- T e. All.

Q. 178. **The following factors increase cardiac output :**
- T a. Pregnancy in late stages
- T b. Histamine
- T c. Eating
- T d. Medulla is removed
- F e. Sitting from lying position

Q. 179. **Coronary blood flow stops during**
- T a. Isovolumetric contraction
- F b. Protodiastole
- F c. End of diastole
- F d. Isometric contraction
- F. e. None.

Q. 180. **Cardiac index in a normal person is :**
- T a. 3.2
- F b. 2.1
- F c. 4.6
- F d. 5.9
- F e. 2.3

Q. 181. **Blood flow in ml/100 gm/min is maximum in :**
- T a. Kidneys
- F b. Liver
- F c. Heart
- F d. Skin
- F e. All.

Q. 182. **The average coronary blood flow in human being at rest is % of cardiac output :**
- T a. 4 - 5%
- F b. 5 - 10%
- F c. 10 - 15%
- F d. 15 - 20%
- F e. 2 - 4%

Q. 183. **The organ with maximum O_2 consumtion per minute**
- T a. Liver
- F b. Brain
- F c. Skeletal muscle
- F d. Heart
- F e. Skin.

Q. 184. **Liver has the maximum O_2 consumption (51 ml/min), the next organ to have the maximum O_2 (ml/min) is :**
- T a. Skeletal muscle
- F b. Heart
- F c. Brain
- F d. Kidney
- F e. Skin.

Q. 185. **The renal blood flow (in ml/minute) is :**
- T a. 1260
- F b. 250
- F c. 800
- F d. 1500
- T e. 1100

Q. 186. **Under resting condtilions, the cardiac output is about ..... L/minute**
- T a. 5.25
- F b. 2
- F c. 4
- F d. 7.5
- F e. 4.5

Q. 187. **Blood supply of liver in ml per minute is**
- T c. 1500
- F a. 800
- F b. 1200
- F d. 1800
- F e. 900

Q. 188. **Work performed by the left ventricle is geater than that performed by the right ventricle due to differences in**
- T a. Arterial pressures
- F b. Blood velocity
- F c. Stroke volume
- F d. Atrial pressures
- F e. None.

Q. 189. **What increases the stroke work done by left ventricle?**
- T a. Systemic hypertension
- T b. Increased sympathetic tone in heart
- T c. Aortic stenosis
- T d. Aortic insufficiency
- T e. All of the above

Q. 190. **Linear velocity of blood at normal cardiac output in the aorta is**
- T a. 32 cms /second
- F b. 64 cms /second
- F c. 8 cms /second
- F d. 50 cms /second
- F e. 18 cms /second.

Q. 200. **Cardiac output in L/min divided by heart rate equals**
- T c. Mean stroke volume
- F a. Cardiac efficiency
- F b. Cardiac index
- F d. Mean arterial pressure
- F e. None.

Heart Rate

Q. 201. **Heart rate**
- T a. is usually increased in hyperthyroidism.
- T b. rises after a meal.
- T c. is usually low amoung the athlets during resting conditions.
- F d. decreases in hypotension.
- F e. decreases after infusion of adrenaline.

Q. 202. **The variation of heart rate is mainly brought about by**
- T a. vagal tone.
- F b. venous return.
- F c. sympathetic stimulation.
- F d. CO_2 excess.
- F e. O_2 lack.

Q. 203. **Heart rate is accelerated by**
- T a. hypoxia
- T b. fever
- T c. inspiration
- F d. fear.
- F e. expiration

Q. 204. **The dicrotic notch on the aortic pressure curve is caused by**
- T a. closure of the aortic valve
- F b. closure of the pulmonary valve
- F c. rapid filling of the left ventricle.
- F d. closure of the mitral valve
- F e. closure of the tricuspid valve

Q. 205. **During exercise**
- T a. heart rate is increased
- T b. sympathetic discharge increases
- T c. venous return increases
- F d. O_2 uptake by the exercising muscle decreases
- F e. total peripheral resistance increases

Q. 206. **Blood pressure increases and heart rate decreases in response to**
- T a. increased intracranial pressure.
- F b. decreased intracranial pressure
- F c. exercise.
- F d. increased body temperature.
- F e. exposure to high altitude.

Q. 207. **Murmurs (or bruits) may be detected by auscultation**
- T a. over dilatations in arteries
- T b. over constrictions in arteries
- T c. in young adult in severe anaemia.
- T d. over vessels in which there is turbulence
- F e. over large arteries in healthy adults

Q. 208. **Maximum heart rate with exercise**
- T a. 200
- F b. 120
- F c. 140
- F d. 160
- F e. 72

Q. 209. **Occlusion of common carotid artery on both sides leads to**
- T a. Increase in HR & BP
- F b. Increase in BP & decrease in HR
- F c. Decrease in HR & BP
- F d. No effect on BP & HR
- F e. None.

Q. 210. **In athletes bradycardia is because of**
- T a. Increased vagal tone
- F b. Decreased sympathetic tone
- F c. Cardiac output
- F d. Low venous return
- F e. None.

Q. 211. **In an unacclatimised person suddenly exposed to**

cold atmosphere, changes seen are

T a. Tachycardia
F b. Increase in systolic BP
F c. Shift of blood from shell to core
F d. Non-thermogenic shivering
F e. None.

Pulse

Q. 212. **Following points are to be considered during examination of a pulse**

T a. condition of vessel wall.
T b. rate
T c. volume
F d. peripheral resistance
F e. rhythm

Q. 213. **Radial pulse**

T a. if normal then is called catachrotic pulse.
T b. is normally 60 -90 beats/minute.
T c. coincides with the apex beat.
F d. if normal then is called anacrotic pulse.
F e. if normal then is called dicrotic pulse.

Q. 214. **What is not true of 'a' wave of venous pulsations in neck?**

T a. Occurs just after in carotid artery
F b. Exaggeration in tricuspid stenosis
F c. Abolished in atrial fibrillation
F d. Exaggerated in complete heart block when P wave falls between QRS and T waves
F e. All.

Q. 215. **What is not true for jugular venous pulse?**

T a. Commonly not visible with normal heart
F b. Pressure typically raised in right ventricular failure
F c. Pressure typically raised in partial obstruction of SVC
F d. Pulsations exaggerated in tricuspid incompetence
F e. None.

Heart sound

Q. 216. **The first heart sound is**

T a. produced at the beginning of ventricular systole.
T b. caused by closure of atrioventricular valves.
T c. caused by closure of mitral and tricuspid valves.
F d. caused by closure of aortic and pulmonary valves.
F e. produced at the beginning of ventricular diastole.

Q. 217. **Characteristics of 2nd heart sound are**

T a. it is heard when ventricles are relaxing.
T b. it has higher frequecy.
F c. it is mainly related to turbulence set up by closure of semilunar valves.
F d. its duration is longer than the 1st heart sound.
F e. it is best heard in mitral area.

Q. 218. **The second heart sound differs from the first heart sound in that it is**

T a. heard when the ventricles are relaxing
T b. higher in frequency
F c. best heard at mitral area
F d. longer lasting than the first heart sound
F e. louder, when listened by stethoscope.

Q. 219. **The second heart sound**

T a. corrosponds to the QRS complex of the ECG.
T b. is produced due to closure of the aortic valve.
F c. is longer lasting than the first heart sound.
F d. is produced due to closure of the mitral valve.
F e. corrosponds to the P wave of the ECG.

Q. 220. **Splitting of the second heart sound into two compo nent is enhanced by**

T a. delayed closure of the pulmonary valve.
F b. early closure of the pulmonary valve
F c. prolongation of atrial systole
F d. delayed closure of the aortic valve
F e. delayed closure of the mitral valve

Q. 221. **The 4th heart sound is caused by**

T a. last rapid filling phase of the ventricle
T b. first rapid filling phase of ventricle.
F c. closure of aortic valve
F d. closure of mitral valve
F e. rapid ventricular filling

Q. 222. ***Heart sound heard immediately before the first heart sound when atrial pressure is high**

T a. Fourth
F b. First
F c. Second
F d. Third
F e. None.

Q. 223. **First heart sound occurs during the period of**

T a. Isovolumetric contraction
F b. Isotonic relaxation
F c. Isovolumetric relaxation
F d. Isotonic contraction
F e. None.

Q. 224. **The second heart sound differs from firstheart sound in that**

T a. Has higher frequency
F b. Is ocassionally split
F c. Duration greater than first sound
F d. Due partly to turbulence set up by valve closure.
F e. None.

Q. 225. **First component of first heart sound is usually clearly heard on ventral surface of chest at :**
- T a. 5th intercostal space to left of sternum
- F b. 2nd intercostal space to right of sternum
- F c. 2nd intercostal space to left of sternmum
- F d. 5th intercostal space over sternum
- F e. 4th intercostal space over sternum.

Q. 226. **Dicrotic notch in aortic pressure curve is :**
- T a. Coincident with 2nd heart sound
- F b. Magnified by aortic regurgitation
- F c. Absent in arteriosclerosis
- F d. Of no diagnostic value
- T e. Coincident with 1st heart sound.

ECG

Q. 227. **In the electorcardiogram the**
- T a. T wave is due to ventricular depolarization.
- T b. QRS complex follows the onset of ventricular contraction.
- T c. P wave is due to atrial depolarization.
- F d. T wave is due to ventricular repolarization.
- F e. P wave is due to ventricular depolarization.

Q. 228. **P wave**
- T a. duration is 0.l second.
- T b. is absent in SA nodal heart block.
- T c. is due to atrial depolarization.
- F d. duration is 0.01 second.
- F e. is due to ventricular depolarization.

Q. 229. **P-R interval**
- T a. indicates the atrial deoplarization and conduction A-V node.
- T b. becomes short in paroxysmal supraventricular tachycardia
- T c. is 12 to 20 second.
- T d. becomes prolonged in heart block.
- F e. is 0.6 second.

Q. 230. **QRS complex is**
- T a. due to venticular depolarization.
- T b. prolonged and deformed in bundle branch block.
- T c. 0.08 to 0.10 second long in duration.
- F d. due to atrial repolarization.
- F e. due to atrial depolarization.

Q. 231. **QRS complex indicates**
- T a. ventricular depolarization.
- F b. AV node conduction time.
- F c. atrial repolarization.
- F d. venticular depolarization.
- F e. atrial depolarization.

Q. 232. **The T wave of the ECG is releated to**
- T a. ventricular repolariztion.
- F b. buhdle of His conduction.
- F c. ventricular depolarization.
- F d. atrial repolarization.
- F e. atrial depolarization.

Q. 233. **ST segment indicates**
- T a. ventricular repolarization
- F b. ventricular depolarization and ventricular repolariza tion.
- F c. atrial repolarization
- F d. ventricular repolarization
- F e. atrial depolarization

Q. 234. **P-R interval in the ECG corresponds to**
- T a. Time interval between onset of atrial contraction and onset of ventricular contraction.
- F b. Time delay in the AV Node
- F c. S-A nodal conduction time
- F d. Ventricular depolarisation
- F e. None.

Q. 235. **Electrocardiographic leads designated V_1, V_2 etc refer to**
- T a. Unipolar chest leads
- F b. Unipolar limb leads
- F c. Bipolar limb leads
- F d. Bipolar chest leads
- F e. All.

Q. 236. **A person with eyes closed and mind wandering will have the following wave in ECG**
- T a. Alpha waves
- F b. Beta waves
- F c. Delta waves
- F d. Theta waves
- F e. None.

Q. 237. **Normal QRS interval is**
- T a. 0.08 - 0.1 second
- F b. 0.12 - 0.20 second
- F c. 0.24 - 0.32 second
- F d. 0.05 - 0.08 second
- F e. 0.5 - 0.8 second

Q. 238. **Changes in mean electrical axis of the ventricles may be caused by**
- T a. Muscular necrosis
- T b. Bundle branch block
- T c. Change in body position
- T d. Hypertrophy ot one ventricle
- T e. All.

Blood Presure

Q. 239. **Increased sympathetic drive to the heart**

T a. increases the rate of conduction in purkinje fiber.
T b. increases the rate of impulse generation.
T c. increases the myocardial metabolis
F d. decreases the ejection fraction of the left ventricle.
F e. decreases the coronary blood flow.

Q. 240. **Sympathetic drive to the heart is increased**
T a. in excitement.
T b. in hypotension
T c. in exercise.
F d. during a vasovagal attack.
F e. when parasympathetic drive is increased.

Q. 241. **Sympathetic drive to the heart is increased during**
T a. excitement
T b. exercise
F c. vasovagal attack.
F d. grief
F e. hypertension

Q. 242. **Sympathetic stimulation causes**
T a. increased venous capacitance
F b. increased total peripheral resistance
F c. increased blood pressure
F d. increased heart rate
F e. increased cardiac output.

Q. 243. **Sympathetic drive to the heart is increased**
T a. in excitement.
T b. in exercise
T c. in hypotension.
F d. during sleep.
F e. when parasympathetic drive is decreased.

Q. 244. **Vasoconstriction occurs due to**
T a. norepinerphrine secretion.
T b. formation of angiotensin II.
T c. increased K^+
T d. release of thromboxane A_2
F e. release of CO_2

Q. 245. **Vascular resistance is increased**
T a. when vessel is increased in length.
T b. when visosity is increased.
F c. when vascular radius is halved.
F d. when wall thickness of vessel is increased.
F e. from arteriolar to the capillary bed.

Q. 246. **Arterioles offer more resistance to blood flow due to**
T a. a greater pressure drop along their length.
F b. smaller internal diameters.
F c. a smaller total cross-sectional area.
F d. thick fibrous wall.
F e. richer parasympathertic innervation

Q. 247. **Peripheral resistance increases due to**
T a. dehydration.
T b. vasoconstriction.
T c. increased viscosity of blood.
F d. increased distance of a blood vessel from the heart.
F e. anemia.

Q. 248. **Resistance to blood flow is**
T a. the lowest in capillary.
T b. inversely proportional to diameter.
T c. directly proportional to haematocrit.
F d. directly proportional to diameter.
F e. determined by arterial pressure.

Q. 249. **Arteriolar constriction may result from**
T a. locally released scrotonin.
T b. decreased local temperature.
T c. Increased adrenargic discharge.
F d. the axon reflex.
F e. decreased adrenergic discharge.

Q. 250. **When the radius of the resistance vessels is increased, which of the following is increased?**
T a. capillary blood flow.
F b. viscosity of the blood.
F c. hematocrit.
F d. systolic blood pressure.
F e. diastolic blood pressure.

Q. 251. **When the radius of the resistance vessel is increased**
T a. the diastolic blood pressure will be decreased.
T b. the systolic blood pressure will be increased.
F c. both the systolic and diastolic blood pressures will be increased.
F d. the systolic blood pressure will be decreased.
F e. both the systolic and diastolic blood pressures will be decreased.

Q. 252. **Right atrial pressure**
T a. increases after massive transfusion.
T b. is equal to the atmospheric pressure.
T c. may be as low as 3 to 5 mm Hg after severe hemorr hage.
F d. decreases in heart failure.
F e. increases when the heart pumps strongly.

Q. 253. **Pulse pressure**
T a. is the difference between systolic and diastolic blood pressure.
T b. increases during moderate exercise.
F c. is the differece between mean pressure and diastolic blood pressure.
F d. decreases during severe exercise.
F e. increases during mild exercise.

Q. 254. **Pulse pressure increases**

T a. in patent ductus arteriosus.
T b. when there is greater stroke volume.
T c. during old age.
F d. in hypothyroidism.
F e. due to increased compliance of the arterial tree.

Q. 255. **Mean arterial pressure is**
T a. directly proportional to the total peripheral resistance.
T b. diastolic pressure plus one third of pulse pressure
F c. measured by sphygmomanometer.
F d. arithmetical mean of systolic and diastolic pressure.
F e. diastolic pressure plus two third of pulse pressure

Q. 257. **Diastolic pressure**
T a. is the minimum pressure during ventricular diastole.
T b. is more in standing position.
T c. is 60-90 mm of Hg.
F d. depends on cardiac output.
F e. is more in lying condition.

Q. 258. **In adult in standing position, the mean arterial pressure**
T a. at the heart level is approximately 100 mm Hg.
T b. in a large artery in the head is less than 70 mmHg.
F c. in a large artery in the foot is nearly 60 mm Hg.
F d. does not differ by changing posture from lying to standing position.
F e. is unaffected by changes in emotional state.

Q. 259. **Within physiological limit, an increase in right atrial pressure**
T a. increases cardiac output.
F b. increases heart rate.
F c. decreases renal blood flow.
F d. decreases systemic arterial pressure.
F e. decreases intrathoracic pressure.

Q. 260. **The local blood vessels dilate due to increased concentration of**
T a. sodium ions.
T b. potassium ions.
T c. magnesium ions.
F d. calcium ion.
F e. endothelin.

Q. 261. **Blood pressure increases and heart rate decreases in response to**
T a. increased intracranial pressure.
F b. decreased intracranial pressure
F c. exercise.
F d. increased body temperature.
F e. exposure to high altitude.

Q. 262. **Pressure on carotid sinus leads to**
T a. reflex bradycardia
F b. Brain bridge reflex.
F c. tachycardia
F d. increased cardiac output
F e. increased blood pressure

Q. 263. **Increased pressure within the carotid sinus causes**
T a. reflex bradycardia.
T b. vasodilation.
T c. venodilation.
F d. increased heart rate.
F e. a fall in venous pressure.

Q. 264. **Minute by minute variation of arterial pressure is controlled**
T a. baroreceptor feedback control mechanism.
F b. capillary fluid shift mechanism.
F c. chemorecptor mechenism.
F d. central nervous system ischemic response (CNS)
F e. renin-angiotensin vasconstrictor mechanism

Q. 265. **Baroreceptor reflex mechanism is**
T a. effective in negative chronotropic and inotropic effect on heart
T b. silent until the blood pressure is 60 mm Hg
T c. the rapidly controlled blood plasma regulatory mechanism.
F d. maximally stimulated when blood pressure is 120 mm Hg.
F e. the last ditch of regulation of blood pressure.

Q. 266. **The baroreceptor reflex**
T a. operates in the normal range of artertial blood pressure.
T b. has receptors in the carotid sinus and aortic arch.
F c. results in tachycardia when a person stands up.
F d. involves sympathetic vasodilator cholinergic fibers.
F e. has receptor located in the carotid bodies and aortic bodies.

Q. 267. **Angiotensin II exerts physiological effect on the**
T a. afferent and efferent arteriole of glomerulus
T b. adrenal gland
T c. blood vessels
F d. bone marrow
F e. spleen.

Q. 268. **The stretch receptors related to arterial pressure control are**
T a. baroreceptors.
T b. receptors in the wall of the atria.
T c. receptors in the wall of the pulmonary artery.
F d. chemoreceptors
F e. osmoreceptors.

Q. 268. **The important long term regulators of arterial pressure**

T a. is renin-angiotensin aldosteron mechanism
T b. are chemoreceptor.
T c. is blood volume
F d. is renin-angiotensin mechanism
F e. are baroreceptors

Q. 269. **During moderate exercise**
T a. end-diastolic volume increases.
T b. diastolic blood pressure remains unchanged.
F c. venous return decreases.
F d. both systolic and diastolic pressures increase.
F e. systolic blood pressure decreases.

Q. 270. **Circulatory adjustment occurs during exercise by**
T a. increasing the cardiac output.
T b. increasing the sympathetic activity over heart.
T c. increasing the arterial pressure.
F d. decreasing the total peripheral resistance.
F e. decreasing the myocardial force of contraction

Q. 271. **Pulmonary wedge pressure corresponds to**
T a. left atrial pressure
F b. right atrial pressure
F c. palmonary venous pressure.
F d. right ventricular pressure
F e. left ventricular pressure

Q. 272. **Vasomotor center is**
T a. in the medulla.
T b. inhibited by impulses from baroreceptors
F c. stimulated by Frank starling machanism
F d. inthepons.
F e. inhibited by impulses from chemoreceptor.

Q. 273. **Autoregulation is not present in**
T a. skin
F b. kidney
F c. brain
F d. liver
F e. myocardium.

Q. 274. **When vasoconstrictor discharge is increased there is**
T a. increased cardiac output
T b. decreased blood stores in the venous reservoirs.
T c. increased arteriotar constriction
T d. increased blood pressure
F e. decreased heart rate

Q. 275. **The basis for Koratkows sounds is due to:**
T a. Arterial turbulence
F b. AV valve closure
F c. Aortic valve closure
F d. Arterial expansion
F e. None.

Q. 276. **Maximum peripheral resistance is seen in**
T a. Arterioles.
F b. Capillaries
F c. Veins
F d. Aorta
F e. Venules

Q. 277. **Major part of total peripheral resistance is due to:**
T a. Arterioles
F b. Medium and small arteries
F c. Venules
F d. Capillaries
F e. Venules

Q. 279. **Doubling the vessel diameters would change the resistance to:**
T a. 1 PRU
F b. 2 PRU
F c. 8 PRU
F d. 6 PRU
F e. 4 PRU

Q. 280. **The arterial pulse pressure in the femoral artery is normally**
T a. Greater than the pulse pressure in the upper aorta
F b. Less than the pulse pressure in the upper aorta
F c. Less than 20 mm Hg
F d. Equal to the pulse pressure in the upper aorta
F e. None of the above

Q. 281. **Peripheral chemoreceptors is stimulated maximally by**
T a. Cyanide
F b. Anaemia
F c. Hypocapnia
F d. Alkalosis
F e. None.

Q. 282. **Carotid body baroreceptor is most sensitive to**
T a. Systolic blood pressure
F b. Mean blood pressure
F c. Diastolic blood pressure
F d. Pulse pressure
F e. None.

Q. 283. **Angiotensinogen is produced by**
T a. Kidney
F b. Liver
F c. Atrium
F d. Hypothalamus
F e. Lungs.

Q. 284. **Occlusion of common carotid artery on both sides leads to**
T a. Increase in HR & BP
F b. Increase in BP & decrease in HR

F c. Decrease in HR & BP
F d. No effect on BP & HR
F e. All.

Q. 285. **Carotid sinus stimulation would result in**
T a. Decreased sympathetic discharge to heart
F b. Decreased vagal activity
F c. Increased heart rate
F d. Increased vasomotor tone
F e. None.

Q. 286. **Carotid sinus afferents pass through**
T a. X nerve
F b. IX nerve
F c. V nerve
F d. VII nerve
F e. VIII nerve

Q. 287. **Baroreceptors mainly act through the**
T a. Parasympathetic system
F b. Sympathetic system
F c. Cerebral cortex
F d. Blood volume
F e. Pons.

Q. 288. **In brain ischaemia, systemic blood pressure rises, this is called:**
T a. Cushing reflex
F b. Monro-Kellie doctrine
F c. Autoregulation reaction
F d. White reaction
F e. None of the above

Q. 289. **Essential hypertension is generally associated with an early increase in**
T a. Cardiac work
F b. Oxygen use
F c. Coronary flow
F d. Cardiac output
F e. All.

Q. 290. **Pulse pressure in a particular vessel is determined chiefly by**
T a. Distensibility
F b. Distance from heart
F c. Frictional characteristics lumen
F d. Cross sectional area
F e. None.

Q. 291. **During blood pressure measurement if the muffled sound does not disappear with return of mercury to 0, the conclusion is**
T a. Low haematocrit
F b. Aortic stenosis
F c. Zero diastolic pressure
F d. Patent ductus arteriosus
F e. None.

Q. 292. **Upto what systolic pressure is the brain capable of autoregulation**
T a. 65 mmof Hg
F b. 55 mmof Hg
F c. 45 mmof Hg
F d. 75 mmof Hg
F e. 85 mmof Hg

Q. 293. **Renin secretion is stimulated by**
T a. Cardiac failure
T b. Low Na^+ in proximal tubule
T c. Sympathetic stimulation
F d. High Na^+ in proximal tubule
F e. None.

Q. 294. **Heart is most sensitive to**
T a. Epinephrine
F b. Nor Epinephrine
F c. Metanephrine
F d. Ephedrine
F e. Atropine.

Q. 295. **Tachycardia in hypertension is caused by stimulation of**
T a. Beta 1 receptor
F b. Alpha 1 receptor
F c. Alpha 2 receptor
F d. Beta 2 receptor
F e. Beta 3 receptor

Q. 296. **Stimulation of baroreceptor leads to**
T a. Decrease in blood pressure and heart rate
F b. Increase in blood pressure and heart rate
F c. Increased intracranial tension
F d. Decreased intracranial tension
F e. None.

Q. 297. **Most potent vasopressor is**
T a. Cortisol
F b. Angiotensin II
F c. Renin
F d. Aldosterone
F e. All.

Q. 298. **In hypertension, there is**
T a. Sodium retention
F b. Reflex vasoconstriction
F c. Renal afferent arteriolar dilatation
F d. Water retention
T e. Ca retention.

Q. 299. **Which of the following does not have natriuretic actions**
T a. Aldosterone
F b. Natriuretic peptide
F c. Angiotensin

F d. Prednisolone
F e. None.

Applied

Q.300. **Effects of excess potassium ion in ECF on heart are :**
T a. heart may be flaccid.
T b. A-V conduction block may occur.
T c. heart become extremely dilated.
F d. heart rate will be increased.
F e. heart may be spastic.

Q. 301. **Coronary vasodilators released during ischemia of cardiac muscle are**
T a. hydrogen ion.
T b. adenosine.
T c. potassium ion.
F d. bicarbonate ion.
F e. sodium ion.

Q. 302. **Anginal pain due to coronary artery disease**
T a. may be elicited by sudden exposure to cold.
T b. is typically made worse by treatment. which lowers the systemic blood pressure.
T c. may be precipitated by anaemia.
F d. is caused by accumulation of metabolites in the myocardium.
F e. is relieved by sympathomymetic drugs.

Q. 303. **In complete heart block the**
T a. QRS complexes are abnonnal but regular.
T b. atria and ventricles beat independently.
T c. ventricular filling shows beat to beat variability.
F d. atrial beat becomes irregular.
F e. ventricular rate falls below 100 beats/min.

Q. 304. **When the AV bundle is completely interrupted as in complete heart block**
T a. ventricular rate falls below 50/minute.
T b. P-R interval shows beat to beat variability.
T c. ventricular filling shows beat to beat variability
F d. QRS comple shows beat to beat variability.
F e. atrial beat becomes irregular.

Q. 305. **Factors causing hypoeffective heart are**
T a. hypertention.
T b. diphtheritic damage.
T c. cardiac anoxia.
F d. hypertrophy of beau muscle.
F e. nervous stimulation.

Q. 306. **In haemorragic shock, there is a decrease in**
T a. venous return.
T b. coronary flow.
T c. cardiac work.
T d. cardiac output.
F e. plasma CO_2

Q. 307. **During which of the following compensatory reactions does hemorrhage generate?**
T a. vasoconstrictjon
T b. increased secretion of renin.
T c. venoconstrictjon
T d. increased secretion of catecholamjnes
F e. bradycardia

Q. 308. **Stokes-Adams syndrome occurs in**
T a. third degree heart block
F b. right or left bundle branch block.
F c. SA nodal block
F d. first degree heart block
F e. second degree heart block

Q. 309. **Murmurs (or bruits) may be detected by auscultation**
T a. over dilatations in arteries
T b. over constrictions in arteries
T c. in young adult in severe anaemia.
T d. over vessels in which there is turbulence
F e. over large arteries in healthy adults.

Q. 310. **Occlusion of common carotid artery on both sides leads to**
T a. Increase in HR & BP
F b. Increase in BP & decrease in HR
F c. Decrease in HR & BP
F d. No effect on BP & HR
F e. None.

Q. 311. **Hypovolemic shock is characterised by the following**
T a. Hypotension
T b. Cold and clammy skin
T c. Intense thirst
T d. Tachycardia
F e. Inhibition of respiration

Q. 312. **40% loss of blood volume in a patient is best managed by**
T a. Saline infusion
F b. Vasopressor agents
F c. Cardiac stimulants
F d. Intracardiac adrenaline
F e. All.

Q. 313. **All are increased during exercise**
T a. Cardiac output
T b. Venous return
T c. Coronary blood flow
F d. Peripheral vascular resistance
F e. All.

Q. 314. **One of the following is earliest indication of concealed acute bleeding**

T a. Tachycardia
F b. Postural HT
F c. Oliguria
F d. Cold clamy fingers
F e. Sweeting

Q. 315. **Rise of pulmonary arterial pressure is cause by**
T a. Hypoxia
F b. Acidosis
F c. Alkalosis
F d. All of the above
F e. None of the above

Q. 316. **Which is going to best declare the case as that of interatrial septal defect with other cardiac abnormalities?**
T a. Elevated PO_2 in pulmonary artery
F b. Elevated pressure in left atrium
F c. Elevated pressure in right atrium
F d. Systolic murmur
F e. None.

Q. 317. **Ventricular fibrillation**
T a. Follows ventricular tachycardia
T b. Associated with quick fall in cardiac output
T c. Induced by alternating current during vulnerable phase
F d. Induced by alternating current
F e. None

Q. 318. **Left ventricular failure tends to cause**
T c. Presystolic murmur over heart
F a. No breathlessness in lying position
F b. Decrease in ventricular end diastolic pressure
F d. Rise in lung compliance
F e. All of the above.

Q. 319. **What is seen following obstruction in major coronary artery?**
T a. Commonly rise in body temperatrue
T b. Reflex vagal inhibition of heart may further damage the myocardium
T c. Commonly ventricular fibrillation
F d. ST depression commonly in lead II
F e. All of the above.

Q. 320. **The first reactive change to occur after hemorrhage is**
T a. Vasocontriction
F b. Tachycarida
F c. Raised cortisol
F d. Raised adrenaline
F e. None of the above.

7

Respiratory System

Functional Anatomy

Two lungs taken together can be viewed as a trumpet having two separate zones-

i. Conducting

ii. Respiratory zone.

Gaseous exchange occurs in the respiratory zone but not in the conducting zones (also called, dead space). Accordingly the respiratory zone presents a typical histological pattern conducive to the exchange. Mast cells of mucosa secrete histamine (H) when their membrane is perturbed and H_1 receptors are occupied by H → bronchospasm. Mast cells also produce SRS-A, which causes bronchospasm. Bronchial muscles supplied by sympathetic (relaxants = bronchodilator ; β_2 receptors) and parasympathetic (constrictor, muscarinic receptors). Besides, VIP secreting neurons also supply. β_2 stimulants (salbutamol) → bronchodilatation. Blood in pulmonary capillary is separated from air within alveolus by alveolo-capillary membrane (= capillary wall + alveolar wall; average thickness 0.5 mm).

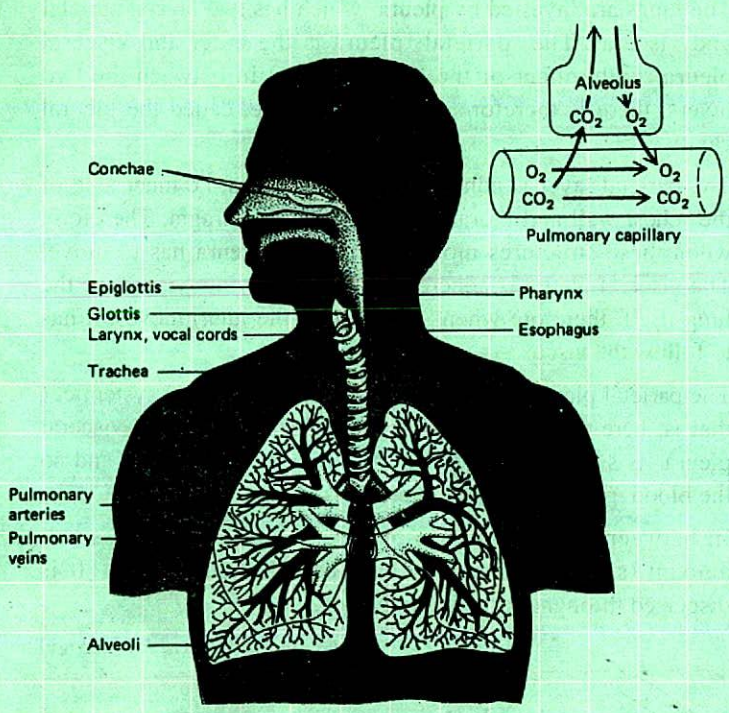


Fig. 7-1. *Respiratory tact or passage.*

Respiratory Tract

The organs which allow the entrance of air into the lungs and exchanges of gases with the blood in the air passages from the nose to the pulmonary alveoli.

Division of respiratory tract :

a. *Upper respiratory tract :* From nose (anterior nares) to the vocal fold. It consist of-
   i. Nose
   ii. Nasopharynx.
   iii. Oropharynx.
   iv. Larynx upto vocal folds.

b. *Lower respiratory tract :* From vocal folds to the alveoli of the lungs. It consist of-
   i. Larynx below the vocal folds
   ii. Trachea
   iii. Two bronchi
   iv. Bronchioles
   v. Terminal bronchioles
   vi. Respiratory bronchioles
   vii. Alveolar duct
   viii. Atria
   ix. Air sac
   x. Alveoli.

Linning epithelium of respiratory system

a. *Trachea & major bronchi :* Pseudostratified ciliated columnar epithelium.

b. *Bronchioles :* Ciliated columnar epithelium. Onwards from respiratory bronchioles : The cilia disappear and the epithelium becomes cubical.

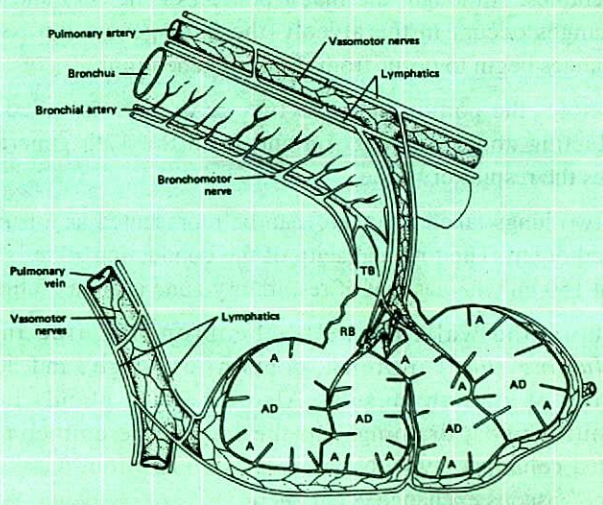


Fig. 7-2. *Respiratory passages or tract.*

c. *Alveolar wall :* Thin, simple squamous type. The linning epithelial cells are of two types.
   i. *Type I cells :* Squamous cells .
   ii. *Type II cells* (also called ***granular pneumocytes***) are interminged with the type I cells. They secrets surfactant a substance which reduce the surface tension in the alveoli. They constitute about 10 percent of the surface area of alveoli.

(Ref. Ganong 22th ed; Page-648, Guyton 11th ed; page-474)

Alveoli

a. *Total numbers*	: 300 million
b. *Total area of the alveolar walls in contact with capillaries in both lungs is about*	: 70 m^2
c. *Space between air and blood*	: 0.5 micro meter

Alveoli communicate with each other by small pores called *pores of khan*. Accessory communication sometimes occur between fine bronchioles and their adjacent alveoli and known as *Lamberts sinuses*.

(Ref. Ganong 22th edition, Page 649)

Conducting and respiratory zone

The whole lung can be divided into two major zones, conducting zone and respiratory zone.

Weibel numbered each generation of tracheobronchial tree.Thus the trachea is generation 0 (zero). The two major divisions of the trachea, viz, the right and left bronchi, constitute the first generation, and so on. In the 16th generation, the bronchi are called the terminal bronchiole.

The 17th generation bronchioles are the respiratory bronchioles. There are three generations of respiratory bronchiole. The alveolar sac is the 23rd and the last generation.

On and from the 17th generation, few alveoli can be found on bronchioles. Although, the major portion of the O_2 and CO_2 exchanges occurs in the alveoli (the 23rd generation), some exchanges begin to occur from the 17th generation.

Therefore the portion upto the 16th generation, is called the conducting zone, whereas on and from the 17th generation begins the respiratory zone.

The two lungs taken together, can be represented as a trumpet shaped organ. The total capacity of the conducting zone is only about 150 ml whereas that of respiratory zone is about 3 liters.

In short, the walls of the tracheobronchial tree in the ***conducting zone*** are thick, contain- cartilage and heavy amount of smooth muscles.Also there are glands in the submucous coat draining into the lumen.The epithelia are ciliated columnar type. No alveolus sprouts from these areas and no gaseous exchange occurs here.

On the other hand, ***respiratory zone*** is a big area containing large number of exceedingly thin walled alveoli, without any mucus secretion. Gaseous exchanges occur through the alveoli of this zone.

It will be seen afterwards that velocity of air flow is high in the conducting zone, whereas it is low in the respiratory zone.

These multiple divisions greatly increase the total cross-sectional area of the airways-

i. Trachea : 2.5 cm^2
ii. Alveoli : 11,800 cm^2.

(Ref. Ganong 21th edition, Page 650 & others)

Pleura

The lungs are invested by pleura which has two layers, parietal and visceral. The parietal pleura is the outer and visceral pleura is the inner of the double layer. In between the two layers, there is therefore a potential space, called the pleural cavity.

The parietal layer is adherent to the parieties, i,e inner side of the chest wall and thoracic side of the diaphragm. Therefore, when these structures move, the parietal pleura has to move. The visceral pleura is adherent to the underlying viscus, i,e the lung itself, therefore when the viscus (the lung) moves, it has to follow the viscus.

The parietal pleura is supplied by vessels which are systemic, (that is, here the blood pressure is higher) whereas the visceral pleura is supplied by vessels of pulmonary circulation and so the blood pressure in these vessels is low.

In between the two layers of pleura there is a very small amount (say about 2ml) of fluid, called ***pleural fluid.*** It is dispersed throughout the pleural cavity.

(Ref. Concise Medical Physiology)

Pulmonary Circulation

Pulmonary blood vessels

Anatomical peculiarities : The pulmonary vascular bed resembles the systemic, except that-

i. The walls of the pulmonary artery and its large branches are about 30% as thick as the wall of the aorta.
ii. The small arterial vessels, unlike the systemic arterioles, are endothelial tubes with relatively little muscle in their walls.
iii. There is also some smooth muscle in the walls of the postcapillary vessels.
iv. The pulmonary capillaries are large, and there are multiple anastomoses, so that each alveolus sits in a *capillary basket.*

(Ganong 22th Edition; page 661)

Pulmonary blood flow

With two quantitatively minor exceptions, the blood put out by the left ventricle returns to the right atrium and is ejected by the right ventricle, making the pulmonary vasculature unique in that

it accommodates a blood flow that is almost equal to that of all the other organs in the body. One of the exceptions is part of the bronchial blood flow. As noted above there are anastomoses between the bronchial capillaries and the pulmonary capillaries and veins, and although some of the bronchial blood enters the bronchial veins, some enters the pulmonary capillaries and veins, bypassing the right ventricle. The other exception is blood that flows from the coronary arteries into the chambers of the left side of the heart. Because of the small physiologic shunt created by those two exceptions, the blood in systemic arteries has a PO_2 about 2 mm Hg lower than that of blood that has equilibrated with alveolar air, and the saturation of hemoglobin is 0.5% less.

(Ganong 22th Edition; page 661)

(Q. 00. Define venous admixture of blood. Does it have any importance?)

Pulmonary blood volume

The blood volume of the lungs is about 450 milli liters, about 9 percent of the total blood volume of the circulatory system. The volume of blood in the pulmonary vessels at any one time is about 1 liter, of which less than 100 ml is in the capillaries. The mean velocity of the blood in the root of the pulmonary artery is the same as that in aorta (about 40 cm/second). It falls off rapidly, then rises slightly again in the larger pulmonary veins.

It takes red cell about 0.75 second to traverse the pulmonary capillaries at rest and 0.3 second or less during exercise.

(Ref. Guyton 11th edition, Page 484; Ganong 22th Edition; page 661)

Pulmonary blood pressure

The entire pulmonary vascular system is a distensible low-pressure system. The pulmonary arterial pressure is about 24/9 mm Hg, and the mean pressure is about 15 mm Hg. The pressure in the left atrium is about 8 mm Hg during diastole, so that the pressure gradient in the pulmonary system is about 7 mm Hg, compared with a gradient of about 90 mm Hg in the systemic circulation. It is interesting that the pressure fall from the pulmonary artery to the capillaries is relatively small and that there is an appreciable pressure drop in the veins.

(Ganong 22th Edition; page 662)

Pressures in the pulmonary artery and vein :

1. *Pressures in the pulmonary artery* :
   a. *Systolic* pulmonary arterial pressure averages approximately 25 mm of Hg in the normal human being,
   b. *Diastolic* pulmonary arterial pressure approximately 8 mm of Hg
   c. *Mean* pulmonary arterial pressure 15 mm of Hg.
2. *Pressures in the pulmonary capillary* : Mean capillary pressure about 7 mm of Hg.
3. *Left atrial and pulmonary venous pressure* : The mean pressure in the left atrium and major pulmonary veins varying from 1 to 5 mm of Hg, averages about 2 mm Hg.

(Ref. Guyton & Hall-11th edition, Page 483, 484)

Trans-pulmonary pressure

It is the pressure difference between the alveolar pressure and the pleural pressure. It is the pressure difference between the alveoli and the outer surface of the lungs, and it is a measure of the elastic forces in the lungs that tend to collapse the lungs at each point of expantion, called the recoil pressure.

(Ref. Guyton & Hall-11th Edition, Page-473)

Capillary pressure

Pulmonary capillary pressure is about 10 mm whereas the oncotic pressure is 25 mm Hg, so there is an inward-directed pressure gradient of about 15 mm Hg which keeps the alveoli free of fluid. When the pulmonary capillary pressure is more than 25 Hg- as it may be, for example, when there is 'back-ward failure' of the left ventricle- pulmonary congestion and edema result. Patients with mitral stenosis also have a chronic, progressive rise in pulmonary capillary pressure and extensive fibrotic changes in the pulmonary vessels.

(Ganong 22th Edition; page 662)

Pulmonary capillary dynamics

Exchange of gases between the alveolar air and the pulmonary capillary blood is discussed in the next chapter. However, it is important for us to note here that the alveolar walls are lined with so many capillaries that in most places, the capillaries almost touch one another side by side. Therefore, it has often been said that the capillary blood flows in the alveolar walls as a "sheet," rather than in individual capillaries.

(Ref. Guyton & Hall-11th edition, Page 487)

Pulmonary capillary pressure : No direct measurements of pulmonary capillary pressure have been made. However, "isogravimetric" measurement of pulmonary capillary pressure, using a technique has given a value of 7 mm Hg. This is probably nearly correct because the mean left atrial pressure is about 2 mm Hg and the mean pulmonary arterial pressure is only 15 mm Hg, so that the mean pulmonary capillary pressure must lie somewhere between these two values.

Length of time blood stays in the capillaries : From histological study of the total cross-sectional area of all the pulmonary capillaries, it can be calculated that when the cardiac output is normal, blood passes through the pulmonary capillaries in about 0.8 second. When the cardiac output increases, this can shorten to as little as 0.3 second. The shortening would be much greater were it not for the fact that additional capillaries, which normally are collapsed, open up to accommodate the increased blood flow. Thus, in only a fraction of a second, blood passing through the alveolar capillaries becomes oxygenated and loses its excess carbon dioxide.

(Ref. Guyton & Hall-11th edition, Page 487)

Capillary exchange of fluid in the lungs, and pulmonary interstitial fluid dynamics : The dynamics of fluid exchange across the lung capillary membranes are *qualitatively* the same

as for peripheral tissues. However, *quantitatively*, there are important differences, as follows :

a. *The pulmonary capillary pressure* is low, about 7 mm Hg, in comparison with a considerably higher functional capillary pressure in the peripheral tissues, about 17 mm Hg.

b. *The interstitial fluid pressure* in the lung is slightly more negative than that in the peripheral subcutaneous tissue. (This has been measured in two ways: by a micropipette inserted into the pulmonary interstitium, giving a value of about -5 mm Hg, and by measuring the absorption pressure of fluid from the alveoli, giving a value of about -8 mm Hg).

c. *The pulmonary capillaries* are relatively leaky to protein molecules, so that the colloid osmotic pressure of the pulmonary interstitial fluid is about 14 mm Hg in comparison with less than one half this in the peripheral tissues.

d. The alveolar walls are extremely thin, and the alveolar epithelium covering the alveolar surfaces is so weak that it can be ruptured by any positive pressure in the interstitial spaces greater than alveolar air pressure (greater than 0 mm Hg), which allows dumping of fluid from the interstitial spaces into the alveoli.

(Ref. Guyton & Hall 11th edition, Page 488)

Interrelations between interstitial fluid pressure and other pressures in the lungs : The balance of forces at the blood capillary membrane as follows :

Forces tending to cause movement of fluid outward from the capillaries and into the pulmonary interstitium :

1.	Capillary pressure	: 7
2.	Interstitial fluid colloid osmotic pressure	: 14
3.	Negative interstitial fluid pressure	: 8
	Total outward force	: *29*

Forces tending to cause absorption of fluid into the capillaries :

1.	Plasma colloid osmotic pressure	: 28
	Total inward force	: 28

Thus, the normal outward forces are slightly greater than the inward forces, providing a mean filtration pressure at the pulmonary capillary membrane; this can be calculated as follows :

	mm Hg
Total outward force	: + 29
Total inward force	: - 28
Mean filtration pressure	: + 1

This filtration pressure causes a slight continual flow of fluid from the pulmonary capillaries into the interstitial spaces, and except for a small amount that evaporates in the alveoli, this fluid is pumped back to the circulation through the pulmonary lymphatic system.

(Ref. Guyton Hall-11th edition, Page 488)

Negative pulmonary interstitial pressure and the mechanism for keeping the 'Alveoli Dry'

One of the most important problems in lung function is to understand why the alveoli do not fill with fluid. One's first impulse is to say that the alveolar epithelium keeps fluid from leaking out of the interstitial spaces into the alveoli. This is not true because there are always a small number of openings between the alveolar epithelial cells through which even large protein molecules as well as large quantities of water and electrolytes can pass.

However, if one remembers that the pulmonary capillaries and the pulmonary lymphatic system normally maintain a slight negative pressure in the interstitial spaces, then it is clear that whenever extra fluid appears in the alveoli, it will simply be sucked mechanically into the lung interstitium through the small openings between the alveolar epithelial cells. Then the excess fluid is either carried away through the pulmonary lymphatics or absorbed into the pulmonary capillaries. Thus, under normal conditions, the alveoli are kept in a "dry" state except for a small amount of fluid that seeps from the epithelium onto the lining surfaces of the alveoli to keep them moist.

(Ref. Guyton & Hall-11th edition, Page 488)

Regulation of pulmonary blood flow

It is unsettled whether pulmonary veins and pulmonary arteries are regulated separately, although constriction of the veins increases pulmonary capillary pressure and constriction of pulmonary arteries increases the load on the right side of the heart. Small arteries several hundred micrometers in diameter are the major site of vascular resistance.

Pulmonary blood flow is affected by both active and passive factors. There is an extensive autonomic innervation of the pulmonary vessels, and stimulation of the cervical sympathetic ganglia reduces pulmonary blood flow by as much as 30%. The vessels also respond to circulating humoral agents. Many of the dilator responses are endothelium-dependent and presumably operate via release of NO. In pulmonary hypertension, there is a deficiency of endothelial NOS.

Passive factors such as cardiac output and gravitational forces also have significant effects on pulmonary blood flow. Local adjustments of perfusion to ventialtion are determined by local effects of O_2 or its lack. With exercise, cardiac output increases and pulmonary arterial pressure rises proportionately with little or no vasodialation. More red cells move through the lungs without any reduction in the O_2 saturation of the hemoglobin in them,and consequently, the total amount of O_2 delivered to the systemic circulation is increased. Capillaries dilate, and previously underperfused capillaries are "recruited" to carry blood. The net effect is a marked incrase in pulmonary blood flow with few if any alterations in autonomic outflow to the the pulmonary vessels.

^{133}Xe can be used to survey local pulmonary blood flow by

injecting a saline solution of the gas intravenously while monitoring the chest. The gas rapidly enters the alveoli that are perfused normally but fails to enter those that are not perfused. Another technique for locating poorly perfused areas is injection of macroaggregates of albumin labeled with radioactive iodine. These aggregates are large enough to block capillaries and small arterioles, and they lodge only in vessels in which blood was flowing when they reached the lungs. Although it seems paradoxic to study patients with defective pulmonary blood flow by producing vascular obstruction, the technique is safe because relatively few particles are injected. The particles block only a small number of pulmonary vessels and are rapidly removed by the body.

When a bronchus or a bronchiole is obstructed, hypoxia develops in the underventilated alveoli beyond the obstruction. The O_2 deficiency apparently acts directly on vascular smooth muscle in the area to produce constriction, shunting blood away from the hypoxic area. Accumulation of CO_2 leads to a drop in pH in the area, and a decline in pH also produces vasoconstriction in the lungs, as opposed to the vasodilation it produces in other tissues. Conversely, reduction of the blood flow to a portion of the lung lowers the alveolar PCO_2 in that area, and this leads to constriction of the bronchi supplying it, shifting ventilation away from the poorly perfused area.

Systemic hypoxia also causes the pulmonary arterioles to constrict, with a resultant increase in pulmonary arterial pressure.

(Ref. Ganong 22th edition, Page 663)

Pulmonary edema

Pulmonary edema occurs in the same way that edema occurs elsewhere in the body. Any factor that causes the pulmonary interstitial fluid pressure to rise from the negative range into the positive range will cause sudden filling of the pulmonary interstitial spaces and alveoli with large amounts of free fluid.

The most common causes of pulmonary edema are as follows :

1. *Left-sided heart failure* or *mitral valvular disease* with consequent great increases in pulmonary venous pressure and pulmonary capillary pressure and flooding of the interstitial spaces and alveoli.
2. *Damage to the pulmonary capillary membrane* caused by infections such as pneumonia or by breathing noxious substances such as chlorine gas or sulfur dioxide gas.

Each of these causes rapid leakage of both plasma proteins and fluid out of the capillaries and into both the lung interstitial spaces and the alveoli.

(Ref. Guyton & Hall-11th edition, Page 488)

Pulmonary edema safety factor : In experiments in animals, it has been found that the pulmonary capillary pressure normally must rise to a value at least equal to the colloid osmotic pressure of the plasma inside the capillaries before significant pulmonary edema occurs. Remember that every time the left atrial pressure rises to high values, the pulmonary capillary pressure rises to a level 1 to 2 mm Hg greater than the left atrial pressure. As soon as the left atrial pressure rose above 23 mm Hg (With the pulmonary capillary pressure above about 25 mm Hg), fluid began to accumulate in the lungs; fluid accumulation increased even more rapidly with further increases in capillary pressure. Yet below 25 mm Hg pulmonary capillary pressure, there was no significant change in pulmonary fluid. The plasma colloid osmotic pressure in dogs is almost equal to this 25 mm Hg critical pressure level. Therefore, in the human being, who normally has a plasma colloid osmotic pressure of 28 mm Hg one can predict that the pulmonary capillary pressure must rise from the normal level of 7 mm Hg to more than 28 mm Hg to cause pulmonary edema, giving a safety factor against pulmonary edema of about 21 mm Hg.

Safety factor in chronic condition : When the pulmonary capillary pressure remains elevated chronically (for at least 2 weeks), the lungs become even more resistant to pulmonary edema because the lymph vessels expand greatly, increasing their capability of carrying fluid away from the interstitial spaces perhaps as much as 10-fold. Therefore, in patients with chronic mitral stenosis, pulmonary capillary pressures of 40 to 45 mm of Hg have been measured without the development of lethal pulmonary edema.

(Ref. Guyton & Hall-11th edition, Page 488, 489)

Broncho pulmonary segment

Each tertiary bronchus and its ramifications and the aleveoli connected with them, constitute a broncho-pulmonary segment, which is self-contained, functionally independent unit of lung tissue. It has its own blood, lymph & nerve supply and connective tissue investment. This is of surgical importance in dissection of a portion of the lung in diseased condition.

There are ten bronchopulmonary segments in the right lung & nine in the left lung. The medial basal or cardiac segment is absent in the left lung.

Broncho vascular units : Each segmental bronchus and its ramifications are not associates with independent vascular pattern, each having its own artery and being separate from its neighbours.

Lung unit/Primary lobule/Respiratory unit : The functional unit of lung, which is the clusters of structures around a single respiratory bronchiole.

It comprises :

i. A single respiratory bronchiole
ii. Five or six alveolar ducts.
iii. Atria
iv. Three to six alveolar sacs.

There are about 300 million alveoli in the two lungs, each alveolus having an average diameter of about 0.2 millimeter.

(Guyton & Hall-11th Edition)

Function of the lungs

A. ***Respiratory function*** :

1. *Gaseous exchanges :* Carriage of oxygen from the lungs to the site of tissue respiration for sub-sequent utilization and also carriage of CO_2 from that site to the lung alveoli for elimination.
2. *Metabolic function :* Oxygen is essen-tial for maintenance of metabolism in the tissue. Aerobic metabolism cannot take place in the abscence of oxygen.
3. *Excretion :* It excretes volatile substancess like ammonia, keton bodies, essential oils, alcohols, water vapours etc.
4. *Maintenance of acid-base balance :* This is done chiefly by adjusting the amount of CO_2 elimination, the normal P^H of the body fluid is 7.4. Any change in the P^H causes alteration in the rate and depth of breathing.
5. *Maintenance of temperature balance :* When water is transformed into gaseous form, heat is absorbed, so heat is lost through water vapours. About 10% of body heat is changed in this way.
6. *Maintenance of water balance* : 600-800 ml of water per day is lost as water vapour during expiration.
7. *Role of respiration on circulation :*
   a. During inspiration the intrathoracic pressure falls and intra-abdominal pressure rises, which helps in return of blood & lymph.
   b. Respiration affect heart rate & cardiac output through nervous mechanism. So changes in respirartion causes change in circulation.
   c. Blood pressure increases during the later part of inspiration & early part of expiration. During the remaining period blood pressure falls.
8. *Homeostatic function :* It helps in maintenance of homeostasis of the internal environment of the body.

B. ***Non-respiratory function of lungs*** :

i. Metabolic function.
ii. Excretory function.
iii. Maintenance of acid base balance.
iv. Maintenace of temperature balance.
v. Maintenance of water balance.
vi. Role on circulation.
vii. Maintenance of homeostasis of the internal environment of the body.
viii. *Lung defense mechanisms* :
   a. They humidify and cool or warm the inspired air. So that even very hot or very cold air is at or near body temperature by the time it reaches the alveoli.
   b. Bronchial secretions contain secretory immunoglobulins (IgA) and other substances that help to resist infection and maintain the integrity of the mucosa. In addition, the epithelium of the paranasal sinuses appears to produce NO, which is bacteriostatic and helps prevent infection.
   c. The Pulmonary alveolar macrophages (PAMS dust cell) are important components of the pulmonary defense mechanism.They are actively phagocytic and ingest inhaled bacteria and small particles.
   d. Various mechanism operate to prevent foreign matter from reaching the alveoli. The hairs in the nostrils strain out many particles larger than 10 mm in diameter.
   e. Particles 2-10 mm in diameter generally fall on the walls of the bronchi as the air flow slows in the smaller passages. There they initiate reflex brochial constriction and coughing.
   f. The epithelium of the respiratory passages from the anterior third of the nose to the begining of the respiratory bronchioles is ciliated, and the cilia beat at a frequency of 1000-1500 cycles per minute, is capable of moving particles at a rate of at least 16 mm/min. Particles less than 2 mm in diameter generally reach the alveoli, where they are ingested by the macrophages.

(Ref. Ganong 22th edition, Page 664 & others)

C. ***Biologically active substances metabolized by the lungs***
(Metabolic and Endocrine function of the lungs) :

a. Synthesized and used in the lung surfactant.
b. *Synthesized or stored and released into the blood* :
   Prostaglandins
   Histamine
   kallikrein.
c. *Partially removed from the blood* :
   Prostaglandins
   Adenine nucleotides
   Nor epinephrine
   Bradykinin
   Serotonin
   Acetylcholine
d. *Activated in the lungs* :
   Angiotensin-I → Angiotesnion-II.

(Ref. Ganong.22th edition, Page 665)

Function of the nose :

The nasal passage (nose) play for the conduction of air and also as efficient air conditioning and filtering units. Thus -

1. The dust particles and bacteria become cought up in the nasal mucous and are removed.
2. The air is cooled down and is made moist.
3. The sense organ of smell is situated in the nose & the odour of the inspired air can be easily taken.

Respiration

(Pulmonary ventilation)

Definition : Respiration is a physiological process which means the transport of O_2 from atmosphere to the body cell for oxidation of the ingested food materials and elemination of CO_2 and other volatile metabolic end products from the cell to the atmosphere.

Phages of respiration : Respiration has two phases -

A. *Inspiration (Active process) :* It means intake of air into lungs. Its duration is about 2 second.

B. *Expiration (passive process) :* It means output of air from lungs. Its duration is about 3 second.

Types of respiration : Respiration are of two types -

1. *External respiration :* Intake of O_2 and removal of CO_2 from body is called external respiration. It include four steps :
   a. Pulmonary ventilation : It means inflow and outflow of air between alveoli and atmosphere.
   b. Diffusion of O_2 and CO_2 between alveoli and blood.
   c. Transport of O_2 to the cells and CO_2 from the cells to the lungs.
   d. Regulation of respiration.
2. *Internal respiration :* The utilization of O_2 and production of CO_2 by cells and the gaseous exchanges between the cells and their fluid medium.

(Ref. Guyton 11th & Ganong 22th edition)

Rate of respiration : It is the total number of respiration per unit time. It is counted in minute. The normal rate of respiration varies in accordance with age, sex, size, work, rest & sleep.

Respiratory rate at different age groups :

Age in years	*Respiratory rate per minute*
At birth	14-60
First years	25-35
2-4 years	20-30
5-14 years	20-25
Adult (male)	10-18
Adult (Female)	10-18

Conditions increase rates of respiration : Rate of respiration is usually proportional to the level of metabolism. It increased in-

I. *Physiological factors* :
   1. Nervous excitement
   2. Muscular exercise.
   3. High altitude
   4. Increased temperature

II. *Chemical factors* :
   1. Increased CO_2
   2. Decreased O_2

III. *Pathological factors* :
   1. Fever
   2. Defective aeriation of blood.

Conditions decrease rates of respiration :

1. Opium
2. Barbiturate poisoning.

NB. Ratio between resipration & arterial pulse in health is 1 : 4. It altered in -

1. Pneumonia (1 : 1)
2. Narcotic poisoning (1 : 6).

Muscles of respiration

Movement of the diaphragm accounts for 75% of the change in intrathoracic volume during quiet inspiration. Attached around the bottom of the thoracic cage, this muscle arches over the liver and moves downward like a piston when it contracts. The distance it moves ranges from 1.5 cm to as much as 7 cm with deep inspiration.

(Ganong 22th Edition; page 652)

A. ***Muscles of inspiration :***
   1. *In quite inspiration :*
      i. *The diaphragm* (accounts 75% of the change in intrathoracic volume during qiute inspiration) : Contraction of the diaphragm pulls the lower surfaces of the lungs downward. The distance it moves ranges from 1.5 cm to as much as 7 cm with deep inspiration.
      ii. *External intercostal muscle* : When the external intercostals contract they elevate the lower ribs. This pushes the sternum outward and increases the antero-posterior diameter of the chest. The transverse diameter also increases, but to a lesser degree.
   2. *In forcefull inspiration :* (Additional muscles)
      i. Sternoclidomastoid muscles - which lift upward on the sternum.
      ii. Scaleni - which lift the first two ribs.
      iii. Anterior serrati - which lift many of the ribs.
      iv. Scalenus posterior
      v. Latissimus dorsi muscle.

B. ***Muscles of expiration :***
   1. *In quite expiration :* Does not involve any muscle. It occurs due to-
      a. Elastic recoil tendency of the lungs and chest wall and abdominal structures which compresses the lungs.
      b. Elastic forces exerted by the surface tension of the fluid lines the inside walls of the alveoli and lung air spaces.

2. *In forcefull expiration :* (Additional muscles)
   i. Abdominal recti
   ii. Internal intercostals
   iii. Serratus posterior inferior muscle.

(Ref. Ganong 22th edition, P-652; Guyton 11th ed, P-471 & others)

Pressure related to respiration

i. Intrapleural pressure.
ii. Intrapulmonary or intra-alveolar pressure.
iii. Intra abdominal pressure.

1. *Intrapulmonary pressure (alveolar pressure) :* It is the pressure within the alveoli of lungs. It is due to contraction and expansion of the lungs during pulmonary ventilation. During inspiration it becomes about (-)1 cm of H_2O. and in expiration it become (+)1 cm of H_2O.

   When glottis is open and no air is flowing into or out of the lungs, the pressure in all parts of the repiratory tree, all the way to the alveoli are all equal to atmospheric pressure , which is considered to be 0 centimeter of water pressure.

2. *Intrapleural pressure :* The potential space between the two layers of pleura contains a thin film of fluid keep the pleura apposed to each other by hydrolytic traction. This force of traction is called intrapleural pressure. It is normally a slightly negative pressure.The normal pleural pressure, at the beginning of inspiration is about (-)5 centimeters of water that is required to hold the lungs open to their resting level. During normal inspiration the expansion of the chest case pulls the surface of the lungs with still greater force and creats a still more negative pressure down to and average of about -7.5 centmeters of water.

(Ref. Guyton 11th edition; page-472)

N.B. Intrapleural pressure : (-) 2.5 to (-) 6 mm of Hg.

(Ref. Ganong 22th edition)

Difference between intrapleural pressure and intrapleural fluid pressure :

Intrapleural pressure	*Intrapleural fluid pressure*
1. It is the amount of negative pressure in the pleural space required to prevent the collapse of the lungs.	1. It is the force of traction between the two pleura.
2. It is the sum total of intrapleural fluid pressure & pleural surface pressure (-10 +6) -4 mm of Hg.	2. It is due to absorption of intrapleural fluid.
3. It is - 4 mm of Hg.	3. It is -10 mm of Hg.
4. It varies with the phage of respiration.	4. It varies with the rate of suction.

Explain- the intrapleural pressure is always negative :

Intrapleural pressure is alwas negative due to continual absorption of fluid or air that try to enter inside the intrapleural space. In addition, the intrapleural fluid contains a muco-polysaccharides which is continually absorbed by the pleural capillaries due to their low capillary pressure (7mm of Hg). This absorbtion creates a partial vacume and produces a negative pressure.

Recoil tendency of lung

The lungs have a continual elastic tendency to collapse and therefore to pull away from the chest wall. This is called the recoil tendency of lungs.

Causes :

i. Elastic fibres of the lungs that are stretched during inspiration and therefore attempt to shorten the lungs.
ii. The surface tension of the fluid lining the alveoli has a elastic tendency to collapse alveoli of the lungs.

This recoil tendency is prevented by :

i. The negetive intrapleural pressure.
ii. Presence of surfactant that reduces surface tension of the fluid lining the alveoli.
iii. Presence of residual volume.

(Ref. Guyton & Hall-11th edition)

Surfactant

Surfactant is a lipo-protein mixture secreted by the special surfactant secreting cells (type II granular pneumocytes) of alveolar epithelium. This mixture contains the phospholipid dipalmitoyl lecithin.

Composition :

Component	*Percent of surfactant*
Dipalmitoylphosphatidylchonile	62
Phosphatidylglycine	5
Other phospholipids	10
Neutral lipids	13
Proteins	8
Carbohoidrate	2

Formation & machenism of surfactant : Lamellar bodies (LB) are formed in type II alveolar epithelial cells and secreted by exocytosis. The released lamellar bodies is converted to tubular myelin (TM), and the TM is probably the source of the phospholipid surface film (SF).Some surfactant is taken up by alveolar macrophages, but more is taken up by endocytosis in type II epithelial cells.

Importance of surfactant :

i. Dipalmitoyl lecithin of surfactant decreases the surface tension of the fluid lining the alveoli thus prevents the collapsing of lungs.
ii. It helps in the expansion of lungs of a new born babies.

iii. It stabilizes the size of alveoli.

iv. It prevents the accumulation of edema fluid in the alveoli.

(Ref. Guyton 11th,edition, page-474; Ganong 22th edition, page-656)

Hyaline membrane disease

A few newborn babies, especially premature babies, do not secrete adequate quantities of surfactant, which makes lung expansion difficult. So, most of them die soon after birth because of inadequate ventilation. This condition is called hyaline membrane disease or respiratory distress syndrom.

(Ref. Guyton & Hall-11th edition)

Compliance

Definition : The extent to which the lungs expand for each unit increase in transpulmonary pressure is called their compliance.

It is determined by the elastic forces of the lungs-

1. The elastic forces of the lungs tissue itself.
2. The elastic force caused by the surface tension of the fluid that lines the inside walls of the alveoli and other lung air spaces. It accounts about two thirds of the total elastic forces in the normal lungs.

or

The expansibility of lungs and thorax is called compliance. This is expressed as, "the volume increase in the lungs for each unit increase in alveolar pressure or for each unit decrease in pleural pressure".

The normal total compliance of lungs together averages 200 ml/cm of water pressure. It means, "every time the alveolar pressure is increased by 1 cm of water the lungs expand 200 ml.

Factors that cause abnormal compliance :

i. Any condition that destroy the lung tissue, causes it to become fibrotic or edematous, blocks the bronchioles, impedes lung expansion and contraction causes decreased lung compliance.

ii. Deformities of chest such as kyphosis, severe sceliosis decreases chest compliance.

iii. Fibrotic pleurisy, paralized or fibrotic muscle reduces the chest compliance.

(Ref. Guyton & Hall-11th edition, page-474)

Work of breathing

During normal breathing contraction of respiratory muscle required only in inspiration, not in expiration which is a passive process caused by the elastic recoil of lungs and chest wall structures. So, the amount of work performed by the respiratory muscle to cause inspiration is called work of breathing.

It is divided into three fractions :

1. *Compliance work :* The work that is required to expand the lungs against the elastic forces is called compliance work.
2. *Airway resistance work :* The work that is required to over come the resistance to airflow through the respiratory passage .
3. *Tissue resistance work :* The work that is required to overcome the viscosity of the lungs and chest cage is called tissue resistance work.

(Ref. Guyton 10th edition, page-435)

Ventilation

Ventilation is of two types :

i. Pulmonary ventilation, and

ii. Alveolar ventilation.

i. *Pulmonary ventilation* : Pulmonary ventilation is the volume of air that is exchanged (i.e. inspired or expired) between the atmosphere and the lungs per minute. It is also called minute ventilation (V_E).

$V_E = V_T \times f$ (Here, VE = minute ventilation

$= 500 \times 12$ VT = tidal volume (averages 500 ml)

$= 6$ litres/minute. f = frequency of respiration/ minute = 12- 15/minute).

In a normal man at rest the V_E is of about : 6 - 7 L /minute.

ii. *Alveolar ventilation* : Alveolar ventilation is the volume of air that enters into the respiratory zone per minute and participates in the gas exchange.

During inspiration first 350 ml of the tidal volume (500 ml) with each breath enters into the alveoli (i.e. gas exchange area) and last 150 ml of the tidal volume remains in the conducting zone (dead space) of the respiratory tract. So, alveolar ventilation (V_A) per minute can be calculated as follows :

$V_A = (V_T - V_D) \times f$ Here, VA = alveolar ventilation

$= 350 \times 12$ VT = tidal volume : 500 ml

$= 4.2$ litres/minute. VD = air in the dead space (dead space volume) : 150 ml

f = frequency of respiration/minute = 12-15 / minute.

In a normal man at rest the V_A is of about 4.5-5 L/minute.

Distribution of ventilation : The alveolar ventilation is not evenly distributed throughout the lungs. In the upright position ventilation per unit lung -volume is greater at the base of the lung than at the apex, but in the supine position this difference tend to disappear. The unequal distributions of the ventilation are due to :

i. Intrapleural pressure is more subatmospheric (i.e. negative) at the apex than at the base

ii. The lung is more expanded (i.e. percentage of maximum lung volume is greater) at the apex than the base, and when the lungs is initially more expanded- the ventilation will be less.

Alveolar perfusion

The total pulmonary blood flow is approximately 5.5 litres/minute at rest. The distribution of pulmonary circulation at different zones of the vertical lungs depends on alveolar pressure (P_A), pulmonary artery pressure (Pa), and pulmonary venous pressure (Pv).

i. Zone 1 (apex) : PA > Pa. Pulmonary artery pressure is normally just sufficient to maintain perfusion. If P_A increased or Pa is reduced, no gas exchange occurs.

ii. Zone 2 (mid zone) : Pa> P_A > Pv : In this region blood flow occurs due to arterial alveolar pressure gradients. The Pa increase 1 cm H_2O for each cm descent from the apex of the lung, but the P_A remain constant. Therefore blood flow increases linearly from top to bottom of zone 2.

iii. Zone 3 (lower zone) : Pa > Pv > P_A : In this region blood flow is determined by the arterio-venous pressure difference.

Therefore in a vertical lung the base is more perfused than the apex of the lung.

Ventilation-Perfusion ratios

i. *Definition* : The ratio of alveolar ventilation to pulmonary blood flow for the whole lung is called ventilation-perfusion ratio.

Normally, alveolar ventilation (V_A)	= 4.2 L/minute
Pulmonary blood flow (Q)	= 5.5 L/minute
So, V_A/Q	= 4.2/5.5
	= 0.8

ii. *Relationships between alveolar ventilation and perfusion* : For efficient gas exchange it is important that there is a match between ventilation of the alveoli (V_A) and their perfusion (Q). In the normal lung the extreme relationships between alveolar ventilation and perfusion are-

i. Ventilation but no perfusion (physiological dead space)

ii. Perfusion but no ventilation (physiological shunting)

iii. *Defferences between alveolar ventilation and perfusion from apex to base of the lungs* : In normal lungs there is a tendency for ventilation not to be matched by perfusion towards the apices, with the reverse occurring at the bases.

a. At the apex : ventilation > perfusion

b. At the base : perfusion > ventilation

But, normally ventilation and perfusion vary in different regions of the normal lungs. The vertical lung base is *over perfused* compared to the ventilation (perfusion > ventilation) and the apex is *under perfused* compared to the ventilation (ventilation > perfusion).

Therefore V_A / Q varies from apex to base of the lungs :

i. VA / Q at apex = 3

ii. VA / Q at base = 0.6

So, in upright lungs V_A / Q is more in the apex than base.

iv. *Interpretation* :

i. The most efficient gas exchange occurs when the V_A/Q is approximately equal to 1.

ii. V_A / Q < 1 : no ventilation but perfusion (physiological shunt occur)

iii. V_A / Q = 0 : no ventilation but perfusion (anatomical shunt occur)

iv. V_A / Q > 1 : ventilation but no perfusion (physiological dead space)

v. V_A / Q ratio affects the PCO_2, and PO_2 in the alveoli. More V_A / Q ratio increases PO_2 in the alveoli and low V_A / Q ratio increases PCO_2 in the alveoli.

vi. V_A / Q is high at the apex (i.e. high PO_2), thus tuberculosis is common in the apical zone of the lungs (high PO_2 favors growth of mycobacteriurn).

Q. 00. **Give the example of ventilation perfusion imbalance with significance.**

Ans. *Ventilation-perfusion imbalance* : Patchy ventilation-perfusion imbalance is by far the most common cause of hypoxic hypoxia in clinical situations.

In disease processes that prevent ventilation of some of the alveoli, the ventilation-blood flow ratios in different parts of the lung determine the extent to which systemic arterial PO_2 declines. If nonventilated alveoli are perfused, the nonventilated but perfused portion of the lung is in effect a *right-to-left shunt*, dumping unoxygenated blood into the left side of the heart. Lesser degrees of ventilation-perfusion imbalance are more common. The underventilated alveoli have a low alveolar PO_2, whereas the overventilated alveoli have a high alveolar PO_2. Consequently, the arterial blood is unsaturated. On the other hand, the CO_2 content of the arterial blood is generally normal in such situations, since extra loss of CO_2 in overventilated regions can balance diminished loss in underventilated areas.

(Ganong 22th edition; page 687)

Respiratory exchange ratio (R)

Definition : Respiratory exchange ratio (R), is the ratio of CO_2 to O_2 at any given time whether or not equilibrium has been reached.

Factors : R is affected by factors other than metabolism.

R can be calculated for reactions outside the body, for individual organs and tissues, and for the whole body. The O_2 consumption and CO_2 production of an organ can be calculated at equilibrium by multiplying its blood flow per unit of time by the arteriovenous differences for O_2 and CO_2 across the organ.

Significance of respiratory exchange ratio (R) : R for the whole body differ in various conditions. For example-

i. *During hyperventilation* : R rises because CO_2 is being blown off.

ii. *During severe exercise* : R may reach 2.00 because CO_2 is

being blown off and lactic acid from anaerobic glycolysis is being converted to CO_2.

iii. *After exercise* : R may fall for a while to 0.50 or less.

iv. *In metabolic acidosis* : R rises because respiratory compensation for the acidosis causes the amount of CO_2 expired to rise.

v. *In severe acidosis* : R may be greater than 1.00.

vi. *In metabolic alkalosis* : R falls.

vii. *During secretion of gastric juice* : the stomach has a negative R because it takes up more CO_2 from the arterial blood than it puts into the venous blood.

(Ganong 22th Edition; page 280)

Normal quiet breathing is maintained by the diaphragm- Explain :

The diaphragm is the principal muscle for quiet breathing. It is dome shaped, and separates the thoracic cavity from the abodominal cavity.

Contraction of the diaphragm helps only in inspira-tion. The vertical descent during quiet normal inspiration, is about 1.5 cm, sufficient to accomodate 500-700 ml of air inside the lungs, which is the tidal volume. Therefore quiet breathing is mainly diaphragmatic.

The diaphragm may descent upto 7 cm, during force full inspiration. In paralysis of the intercostal muscle, the diaphragm maintains the respiration. This diaphragmatic respiration is known as abdominal type of respiration.

Mechanism of Respiration

(Pulmonary ventilation/ respiration or how air enters inside the lungs) :

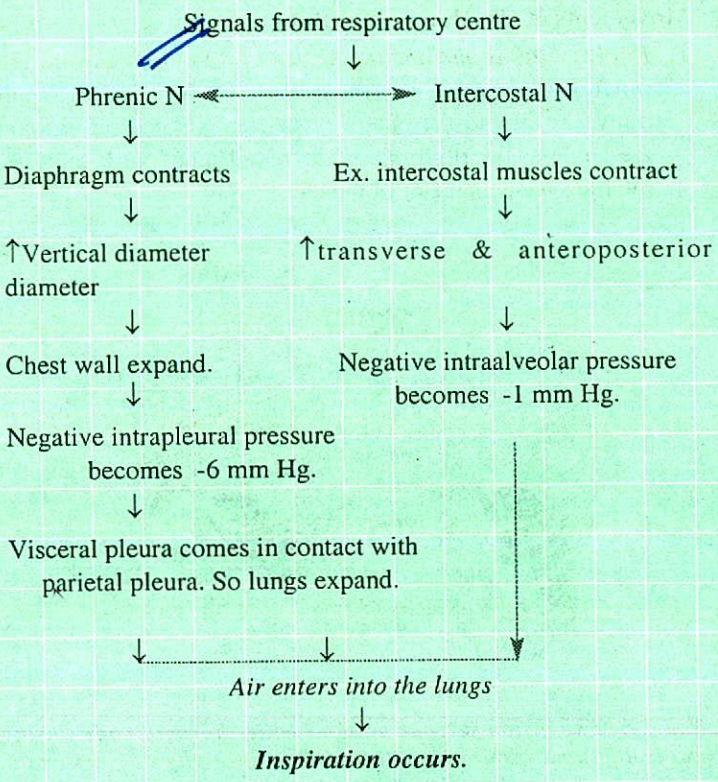
The basic mechanism of respiration (breathing) are expansion and contraction of lungs which can be achieved in two ways :

1. By downward and upward movement of the diaphragm to lengthen or shorten the vertical diameter of chest cavity.
2. By elevation and depression of ribs to increase or decrease the antero-posterior diameter of chest cavity.

During inspiration :

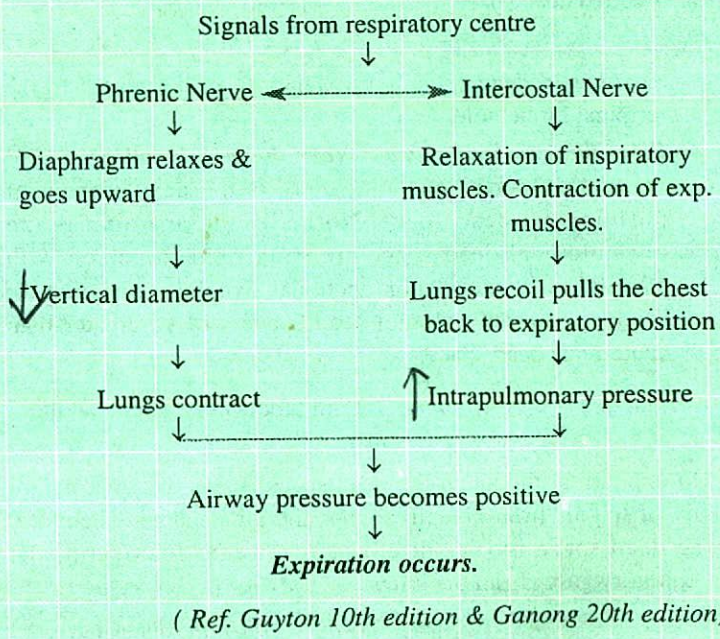
The inspiratory center stimulates and discharge impulses causes contraction of inspiratory muscles. Due to contraction of the diaphragm the vertical diameter of the chest cavity and by the contraction of external intercostal muscles antero-posterior and transverse diameter of the chest cavity increases. This increased chest cavity decrease the negative intrapleural pressure (from -2.5 to -6 mm of Hg or -7.5 cm of H_2O), which then pulls upon the visceral pleura causing enlargement of lungs and respiratory air passages, thereby creating a fall of intra alveolar pressure (-1cm of H_2O) in respect to atmosphere. Then the air will rushes inside the lungs from atmosphere.

(Ref. Guyton & Hall-11th edition & Ganong 22th edition)



During expiration :

Expiration is a passive process. It does not involve muscle except forcefull expiration. It occurs due to elastic recoil tendency of lungs and chest wall and elastic forces exerted by the surface tention of the fluid lies the inside walls of the alveoli and lung air spaces. The elasticity of lungs turn the diaphragm upwards and depress the ribs, the diameter of the chest cavity decreases, intra-alveolar (intra pulmonary) pressure rises which causes expulsion of air from lungs into atmosphere.



(Ref. Guyton 10th edition & Ganong 20th edition)

Movements of ribs during breathing

1. *Bucket handle movment :* In this movement the middle portion of ribs (from 7th to 10th) moves upwards and outwards around the antero-posterior axis passing through the angle of the rib to the costosternal junction. It increases the transverse diameter of the chest cavity.

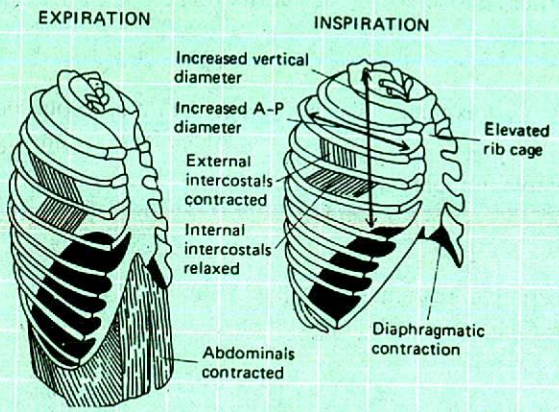


Fig.7-3. *Expansion & contraction of the thoracic cage during expiration and inspiration, illustrating especially diaphragmatic contraction, elevation of the rib cage, and function of the intercostals.*

2. *Pump handle movement :* In this movement anterior ends of the ribs (from 2nd to 6th) move upwards and forwards along the oblique axis passing through the neck of the ribs. It increases antero-posterior diameter of the chest cavity.

Dead Space

The space in the respiratory passage occupied by gas but does not allow in gaseous exchange but only acts as a reserviour of air is called dead space.

Types :

1. *Anatomical dead space :* It extends from the nostril to the terminal bronchiole.
2. *Physiological dead space :* When there is the alternation of ventilation perfusion ratio, there is the development of phsiological dead space. Normally the anatomical and physiological dead space are equal, but in person with partially functional or nonfunctional alveoli in some parts of the lung, the physiologiol dead space will be greater than anatomical dead space.

Normal dead space volume : 150 ml (about) in a young adult man.

On expiration, the air in the dead space is expired first, before any of the air from alveoli reaches the atmosphere. Therefore, the dead space is very disadvantageous for removal of the expiratory gases from the lungs.

(Ref. Guyton & Hall-11th edition, page500)

Dead space air

Definition : The amount of air that enters the respiratory passages but do not take part in the gaseous exchange is called dead space air.

Types :

a. *Anatomical dead space air* : The amount of air that remains in the conducting portion of the respiratory system that is from nose to terminal bronchiole with each phase of respiration is called anatomical dead space air. It is about 150 ml.

Improtance :

i. Saturates the inspired air by water vapour before reaching the alveoli.
ii. Helps in the removing of particles having a size more than 2 micron.

b. *Physiological dead space air* : It is the amount of air that is equal to anatomical dead space air plus the volume of air in the alveoli, having no blood supply. Usually this does not remain in normal condition.

Importance :

i. It gives an indication about the condition of the lungs.
ii. Indicates ventilatoin perfusion ratio.

(Ref. Guyton & Hall-11th edition, page478)

Pulmonary Volumes & Capacities

Pulmonary volumes

1. *Tidal volume :* It is the volume of air inspired or expired with each normal breath. It is about 500 ml.
2. *Inspiratory reserve volume :* It is the extra volume of air that can be inspired over and beyond the normal tidal volume. It is about 3000 ml.
3. *Expiratory reserve volume :* It is the amount of air that can be expired by forcefull expiration after the end of a normal tidal expiration. It is about 1100 ml.
4. *Residual volume :* It is the volume of air still remaining in the lungs after the most forcefull expiration. It is about 1200 ml.

(Ref. Guyton & Hall-11th edition, page 475)

Pulmonary Capacities

1. *Inspiratory capacity :* This is the amount of air that a person can inspired forcefully after a normal tidal expiration. It is about 3500 ml.

   Inspiratory capacity = Tidal volume + inspiratory reserve volume
   = 500 ml + 3000 ml
   = 3500 ml.

2. *Functional residual capacity :* This is the amount of air remaining in the lungs at the end of normal expiration. It is about 2300 ml.

Functional residual capacity = Expiratory reserve volume + residual volume
= 1100 ml + 1200 ml
= 2300 ml.

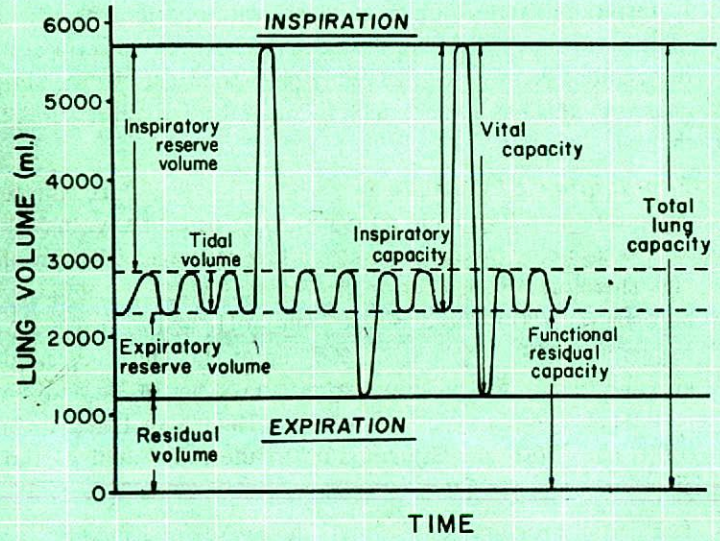


Fig. 7-4. *Diagram showing the lung volume & capacity.*

3. *Vital capacity :* The ***maximum*** amount of air that a person can *expired forcefully after the forcefull inspiration* is called vital capacity. It is about 4600 ml or 4.6 litre.

   Vital capacity = Tidal volume + Expiratory reserve volume + Inspiratory reserve volume.

   = 500 ml +1100 ml + 3000 ml
   = 4600 ml
   = 4.6 litres (male : 3.2-4.6 L; female : 2.9-4.2 L)

4. *Total lung capacity :* It is the maximum volume to which the lungs can be expanded with the greatest possible inspiratory effort.

   It is about 5800 ml.

   Total lung capacity = Vital capacity + Residual volume.
   = 4600 ml + 1200 ml
   = 5800 ml
   = 5.8 litres.

5. *Expiratory capacity :* It is the amount of air that a person can expired forcefully after a normal tidal inspiration.

   Expiratory capacity = Tidal volume + Expiratory reserve volume
   = 500 ml + 1100 ml
   = 1600 ml
   =1.6 litres.

N.B: All the pulmonary volume and capacities are about 20 to 25% less in women than in men and they are obviously greater in large and athlet persons than in small and asthenic persons.

(Ref. Guyton & Hall-11th edition, page476 & others)

Importance of residual volume :

i. It provides air in the alveoli to areate the blood (exchange of O_2 and CO_2) even between breath (expiration and inspiration) thereby prevents the sudden rise and fall of O_2 and CO_2 concentration in blood in each respiration.
ii. It prevents the collapse of alveoli of lungs.

(Ref. Guyton & hall-11th edition)

Vital Capacity

Definition : The ***maximum*** amount of air that a person can *expired forcefully after the forcefull inspiration* is called vital capacity.

Principle of measurement of vital capacity : Vital capacity is measured by spirometer. This consists of a drum inverted over a chamber of water, with the drum counter balanced by a weight. In the drum there is a breathing mixture of gases, usually air or oxygen. A tube connects the mouth with the gas chamber. When one breathes in and out of the chamber the drum rises and falls and an appropriate recording is made on a moving sheet of paper or on the meter.

Factors affecting vital capacity :

A. Air way resistance
B. Force of contraction of respiratory muscles
C. Elastic recoil tendency of the lungs.
D. Others :
   1. *Age :* It is more in young.
   2. *Sex :* 10% less in female due to
      i. Less surface area
      ii. Short thoracic cage
      iii. Less muscular strength.e.g.Adult man-4.6 liter. Adult female- 3.1 liter.
   3. *Posture :*
      Less in lying but more in erect posture due to
      i. Intra abdominal pressure
      ii. Pulmonary vascular blood volume.
   4. Surface area :
      Vital capacity is proportional to surface area.
   5. Anatomical built of the chest : Vital capacity decreases in some chest deformities such as
      i. Barrel shaped chest
      ii. Pigeons chest
      iii. Kyphosis.
   6. Diseases of lung and pleura :
      These decreases vital capacity by decreasing compliance.
   7. Paralysis of respiratory muscles :

Vital capacity decreases as low as 500-1000ml in this condition.

8. Congestive left heart failure :
   Causes pulmonary vascular congesion and edema which then decreases lung compliance and subsequently vital capacity.

Importance of vital capacity :

1. Measurement of the vital capacity give the idea of the condition of lungs i.e the maximum volume of air that can be tackled without any discomfort.
2. Indicates the efficiency in the acts of ventilation.
3. It is important in the lung functions tests as it decerases 500-1000ml after the paralysis of the respiratory muscles.
4. Clinically, it is important for the assesment of the different pulmonary fibrotic disease such as Tuberculosis(TB), Asthma, Emphysema.

Time vital capacity or Force expiratory volume (FEV_1)

Vital capacity is timed that means the percentage of vital capacity that is expired in 1st, 2nd and 3rd sec are determined. Normally FEV_1 is 83%-84% in 1st second; 93% in 2nd sec, 97% in 3rd sec.

The volume of air expired at one second is called *force expiratory volume at one second (FEV_1).*

Importance of FEV : If FEV_1 is found less than 80% in first second then there is obstruction some where in the air passage, such as in asthma.

Gaseous exchange between Lungs & Tissues

Composition of atmospheric, alveolar and expired air

	Atmospheric air (mm Hg.)		*Expired air (mm Hg.)*		*alveolar air (mm Hg.)*	
N_2	597.0	78.26%	563.4	74.9%	569.0	74.5%
O_2	159.0	20.84%	149.3	13.6%	104.0	15.5%
CO_2	0.3	0.04%	0.3	5.3%	40.0	3.6%
H_2O	3.7	0.50%	47.0	6.2%	47.0	6.2%
Total	760.0	100.0%	760.0	100.0%	760.0	100.0%

(Ref. Guyton 10th edition, page454)

Partial pressure :

The partial pressure of a gas in a mixture is the total amount of impaction force of the molecules of that particular gas alone against the surface.

Pressure is caused by the constant impact of kinetically moving molecules against a surface. Therefore, the pressure of a gas acting on the surfaces of the respiratory passages and alveoli is proportional to the summated force of impact of all the molecules striking the surface at any instant. This means that the total pressure is directly proportional to the concentration of the gas molecules.

In respiratory physiology, one deals with mixtures of gases, mainly of oxygen, carbondioxide, nitrogen etc. The rate of diffusion of these gases is directly proportional to the pressure caused by this gas alone, which is called the partial pressure of the gas.

Explanation : Consider air, which has an approximate composition of 79 percent nitrogen and 21 percent oxygen. The total pressure of this mixture at sea level averages 760 mm of Hg. Therefore, 79 percent of the 760 mm of Hg is caused by nitrogen (i.e 760 x .79) about 600 mm of Hg and 21 percent by oxygen (i.e 760 x 0.21) about 160 mm of Hg. Thus the partial pressure of nitrogen in the mixture is 600 mm of Hg and the partial pressure of oxygen is 160 mm of Hg; the total pressure is (600+160) 760 mm Hg, the sum of the individual partial pressure.

The partial pressures of the individual gases in a mixture are designated by the symbols Po_2, Pco_2, PN_2, PH_2o and so forth.

(Ref. Guyton & Hall-11th edition, page-492)

Partial pressure of O_2 (PO_2) :

Definition: Partial pressure of oxygen (Po_2) is the total amount of impaction force of oxygen (O_2) molecules on the surfaces.

Partial pressure of O_2 in various parts of the respiratory system and in the circulatory system is :

1. Lung alveoli : 104 mm of Hg
2. Pulmonary venous end : 104 mm of Hg
3. Arteries : 95 mm of Hg
4. Tissue arterial end : 95 mm of Hg
5. Tissue venous end : 40 mm of Hg
6. Interstitial fluid : 40 mm of Hg
7. Arterial blood entering the lungs or pulmonry arterial end. : 40 mm of Hg.

(Ref. Guyton & Hall-11th edition, page 502)

Partial pressure of CO_2 (PCO_2) :

Definition : Partial pressure of carbondioxide (Pco_2) is the total amount of impaction force of carbondioxide (Co_2) molecules on the surfaces.

PCO_2 in various parts :

1. Tissue : 46 mm of Hg
2. Interstitial fluid : 45 mm of Hg
3. Venous blood : 46 mm of Hg
4. Pulmonary artery : 46 mm of Hg

5. Alveoli : 40 mm of Hg
6. Arterial blood : 40 mm of Hg.

(Ref. Guyton & Hall-11th edition, page 502)

Partial pressure of respiratory gases in inspired and expired air :

Gas	*Inspired air mm Hg*	*Expired air mm Hg*
N_2	596.0	565.0
O_2	158.0	116.0
CO_2	0.3	32.0
H_2O	5.7	47.0

(Ref. Ganong 22th edition, Page 660)

Partial pressure of respiratory gases in circulatory system & alveoli :

Gas	*Alveolar air mm Hg*	*Arteries mm Hg*	*Tissues mm Hg*	*Veins mm Hg*
N_2	573.0	573.0	573.0	573.0
O_2	100.0	95.0	40.0 -	40.0
CO_2	40.0	40.0	46.0 +	46.0
H_2O	47.0	47.0	47.0	47.0

(Ref. Ganong 22th edition, Page 660)

Respiratory Membrane

Gaseous exchange between the alveolar air and the pulmonary blood occurs through the membranes of all the terminal portions of the lungs. These membrane are known as respiratory membrane.

(Ref. Guyton & Hall-11th edition, page 497)

Thickness : 0.3 to 1.0 micrometer, average 0.5 micromter.

Different layer of respiratory membrane :

1. A layer of fluid lining the alveolus and containing surfactant
2. The alveolar epithelium composed of thin epithelial cells.
3. An epithelial basement membrane.
4. A thin interstitial space between the alveolar epithelium and the capillary membrane.
5. A capillary basement membrane that in many places fuses with the alveolar epithelial basement membrane.
6. The capillary endothelial membrane.

(Ref. Guyton & Hall-11th edition, page 497)

Factors affecting gaseous exchange through the respiratory membrane :

1. *Thickness of the membrane :* The rate of diffusion through the membrane is inversely proportional to the thickness of the respiratory membrane. So any factor that increases the thickness of membrane such as edema of lungs, fibrosis of lungs also decrease the diffusion of gas through the membrane.
2. *The surface area of the membrane :* When the total surface area is decreased to approximately one-third to one-fourth normal, exchange of gases through the membrane impeded. So, any factor such as removal of part of lungs, cancer, tuberculus destruction and emphysema that decrease the area of membrane also decreases the rate of gases diffusion.
3. *The pressure difference of the gas between the two sides of the membrane :* When partial pressure of alveolar gas is greater than the pressure of gas in blood, net diffusion from the alveoli into the blood occurs. The opposite phenomenon occur when the pressure of the gas in the blood is greater than the alveolar gas.

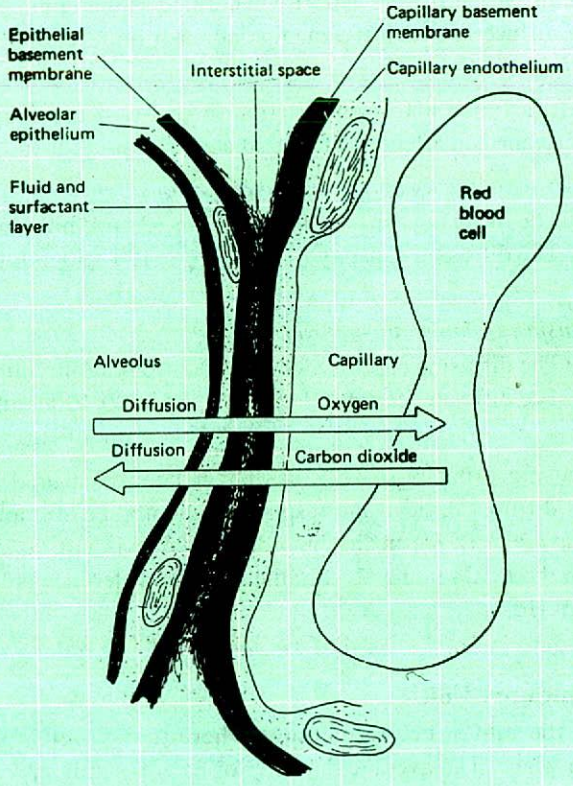


Fig. 7-5. *Ultrastructure of the respiratory membrane.*

4. *The diffusion co-efficient of the gas in the substance of the membrane :* The unit volume of a gas is measured in millimeters which diffuse through 1 sq.m of the membrane per minute when there is a pressure difference of 1 mm of Hg across the membrane is known as diffusion co-efficient.

   It depends on :

   a. Solubility of gases in the fluid of the membrane.

b. The molecular wt.

(Ref. Guyton & Hall-11th edition, page 498)

Factors increasing the thickness of respiratory membrane :

1. Edema fluid in the interstitial space of the membrane and in the alveoli.
2. Fibrosis of the lung.

(Ref. Guyton & Hall-11th edition, page 498)

Factors decreasing the surface area of respiratory membrane :

1. Removal of an entire lung or part of a lung.
2. Emphysema, in which many of the alveoli coalesce, with dissolution of many alveolar wall.
3. Cancer.
4. Tuberculous destruction.

(Ref. Guyton & Hall-11th edition, page 498)

Diffusing capacity of the respiratory membrane

Definition : Diffusing capacity is defined as the volume of a gas that diffuses through the membrane each minute for a pressure difference of 1 mm Hg.

Factors those affect the diffusion through the respiratory membrane can affect diffusing capacity.

Diffusing capacity under resting conditions :

1. The diffusing capacity for O_2 : 21 ml/min/mm of Hg
2. The diffusing capacity for CO_2 : 400-450 ml/min/mm of Hg.

Diffusing capacity during exercise :

1. The diffusing capacity for O_2 : 65 ml/min/mm of Hg
2. The diffusing capacity for CO_2 : 1200-1300 ml/min/mm of Hg.

Diffusing capacity of CO_2 has never been measured because CO_2 diffuses through the respiratory membrane so rapidly that the average PCO_2 in the pulmonary blood is not far different from the PCO_2 in the alveoli, the average difference is less than 1 mm Hg.

(Ref. Guyton & Hall-11th edition, page 498)

Respiratory Unit

It is the unit structure of lungs where the gaseous exchange takes place. The average diameter of each respiratory unit is 25 mm. There are 300 million of respiratory unit in the two lungs. Each respiratory unit composed of respiratory bronchiole, alveolar ducts, atria, and alveolus.

(Ref. Guyton & Hall-11th edition, page 496)

Transport of O_2

Transport of O_2 from alveolar air into tissue cell can be considered in 4 steps :

1. *Diffusion of O_2 from alveolar air into pulmonary capillary* : The partial pressure of oxygen (PO_2) in alveolus is 104 mm of Hg, where as the PO_2 in pulmonary capillary at arterial end is 40 mm of Hg. So, the pressure difference that causes O_2 to diffuse into the pulmonary capillary is (104 - 40) =64 mm of Hg. So, O_2 diffuse into pulmonary blood from alveolar air and the PO_2 of blood become equal to alveolar air by the time the blood has moved a third of the distance through the capillary.
2. *Transport of O_2 in the blood :* O_2 is transported in the blood in two ways :
   i. *In the form of oxy-haemoglobin : About 97% (19.5 ml/100 ml of blood)* of O_2 is carried in chemical combination with haemoglobin in the red cells by the process of oxygenation . The combination of O_2 with Hb is loose and reversible.
   ii. *As physical solution :* The *remaining 3% (0.29 ml/100 ml of blood)* of O_2 is transported in the dissolved state in the water of the plasma and cells.
   The arterial blood that enters the left atrium of heart is 97% saturated with O_2. Because of slight admixture of venous blood that passes through physiological shunts.

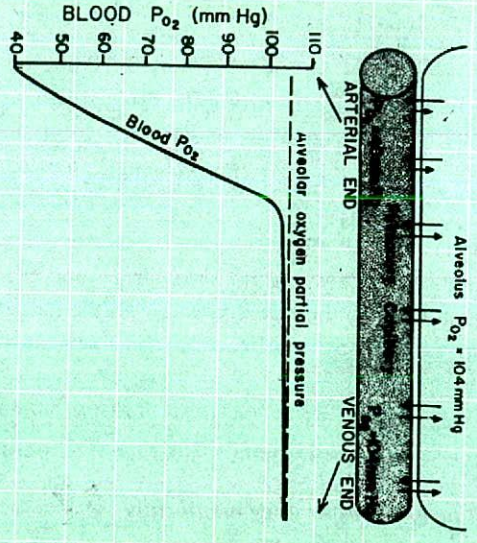


Fig. 7-6. *Uptake of O_2 by the pulmonary capillary blood.*

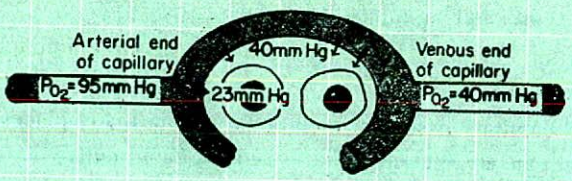


Fig. 7-7. *Diffusion of O_2 from a tissue capillary to the cell.*

3. *Diffusion of O_2 from blood to tissue interstitial fluid* : The blood PO_2 is 95 mm of Hg in tissue arterial end and PO_2 of interstitial fluid is 40 mm of Hg . So, the pressure difference is (95-40) 55 mm of Hg, and causes diffusion of O_2 into interstitial fluid.

4. *Diffusion of O_2 from interstitial fluid into cells* : The PO_2 of interstitial fluid is 40 mm of Hg and PO_2 inside the cell is ranging from 5 to 40 mm of Hg, averaging 23 mm of Hg. Because only 1 to 3 mm of Hg of oxygen pressure is normally required for full support of the chemical processes that use oxygen in the cell, one can see that even this low cellular PO_2 of 23 mm Hg is more than adequate and provides a large safety factor.

(Ref. Guyton 11th edition, P-502, 503; Ganong 22th edition, P-666)

PO_2 in aorta is 95 mm of Hg--explain ?

Ans.

About 98 % of the blood that enters the left atrium from the lung passes through the alveolar capillaries and becomes fully oxygenated that is PO_2 is approximately 104 mm of Hg. Another 2% of the blood leaving the lung passes through the bronchial circulation, which supplies mainly the pulmonary air. Therefore this blood flow represents 'shunt' and its PO_2 is approximately that of normal venous blood about 40 mm of Hg. This blood combines in the pulmonary veins with the oxygenated blood , this mixing of blood is called venous admixture of blood and it causes the PO_2 of the blood pumped by the left heart into aorta to fall to approximately 95 mm of Hg.

(Ref. Guyton 11th edition, page 503)

Oxygen-haemogblin dissociation curve

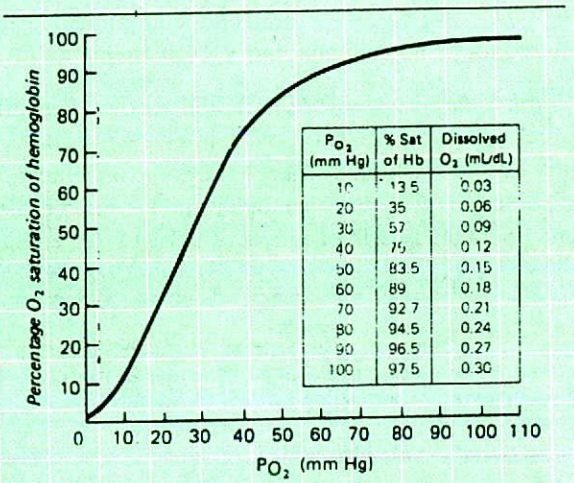
The dissociation of the oxygen from haemoglobin is studied by constructing a graph, where the relation of partial oxygen pressure and the percentage oxygen saturation of Hb in the blood are plotted as abscissa and ordinate, respectively.

Oxygen-hemoglobin dissociation curve is a graphical recording which shows a progressive increase in the *percentage saturation of the hemoglobin that is bound with oxygen as the PO_2 increases*. The curve is constructed by placing the percent saturation of Hb with O_2 at ordinate and tension of O_2 at abscissa.

(Ref. Guyton & Hall-11th edition, page 506)

The oxygen-hemoglobin dissociation curve, the curve relating percentage saturation of the O_2 carrying power of hemoglobin to the Po_2 has a characteristic sigmoid shape. When hemoglobin takes up a small amount of O_2, the R state is favoured and additional uptake of O_2 is facilitated. Combination of the first heme in the Hb molecule with O_2 increases the affinity of the second heme for O_2 and oxygenation of the second increases the affinity of the third, etc, so that the affinity of Hb for the fourth O_2 molecule is many times that for the first.

When blood is equi librated with 100% O_2 (Po_2 = 760 mm Hg), the normal hemoglobin becomes 100% saturated. When fully saturated , each gram of normal hemoglobin contains 1.39 mL of O_2. However, blood normally contains small amounts of inactive hemoglobin derivatives, and the measured value in vivo is lower. The traditional figure is 1.34 mL of O_2. The hemoglobin concentration in normal blood is about 15 g/dL (14 g/dL in women and 16 g/dL in men). Therefore, 1 dL of blood contain 20.1 mL (1.34 mL x 15) of O_2 bound to hemoglobin when the hemoglobin is 100% saturated. The amount of dissolved O_2 is a linear function of the Po_2 (0.003 mL/dL blood/mm Hg Po_2).



P_{O_2} (mm Hg)	% Sat of Hb	Dissolved O_2 (mL/dL)
10	13.5	0.03
20	35	0.06
30	57	0.09
40	75	0.12
50	83.5	0.15
60	89	0.18
70	92.7	0.21
80	94.5	0.24
90	96.5	0.27
100	97.5	0.30

Fig. 7-8. *Oxygen-haemoglobin dissociation curve.*

In vivo, the hemoglobin in the blood at the ends of the pulmonary capillaries is about 97.5% saturated with O_2 (Po_2 = 97 mm Hg). Because of a slight admixture with venous blood that by passes the pulmonary capillaries (physiologic shunt), the hemoglobin in systemic arterial blood is only 97% saturated. The arterial blood therefore contains a total of about 19.8 mL of O_2 per dL: 0.29 mL in solution and 19.5 mL bound to hemoglobin. In venous blood at rest, the hemoglobin is 70% saturated and the total O_2 content is about 15.2 mL/dL: 0.12 mL in solution and 15.1 mL bound to hemoglobin. Thus, at rest the tissues remove about (19.8-15.2) 4.6 mL of O_2 from each deciliter of blood passing through them; (0.29-0.12) 0.17 mL of this total represents O_2 that was in solution in the blood, and the remainder represents O_2 that was librated from hemoglobin. In this way, about 250 ml of O_2 per minute are transported from the blood to the tissues at rest.

$$\frac{4.6 \times 5500}{100} = 247.5 \text{ ml} \quad (\textit{Here, } CO = 5500 \text{ ml})$$

(Ref. Ganong 22th edition, Page-666)

Factors affecting the affinity of hemoglobin for oxygen :

A number of different factors can displace the dissociation curve in one direction or the other. These are-

1. *pH* : When blood becomes slightly acidic, with the pH decreasing from the normal value of 7.4 to 7.2, the oxygen-

hemoglobin dissociation curve shifts to the right. When the curve is shifted in this direction, a higher PO_2 is required for hemoglobin to bind a given amount of O_2.

On the other hand, an increase in the pH to 7.6 shifts the curve to the left and a lower PO_2 is required to bind a given amount of O_2.

2. *Blood temperature :* A rise in temperature decrease the hemoglobin saturation. It shifts the curve to the right. When the curve is shifted in this direction, a higher PO_2 is required for hemoglobin to bind a given amount of O_2.

3. *2,3 - diphosphoglyerate (DPG) :* 2,3 DPG is very plentiful in red cells. It is form from 3-phosphoglyceraldehde by EM pathway. It is a highly charged anion that bind to beta chains of deoxygenated haemoglobin. One mole of deoxy-hemoglobin binds with one mole of 2,3-DPG. In effect,

$HbO_2 + 2, 3\ DPG = Hb\text{-}\ 2, 3\ DPG + O_2$

In this equilibrium, an increase in the concentration of 2,3 DPG shift the reaction to the right, causing more O_2 to be liberated.

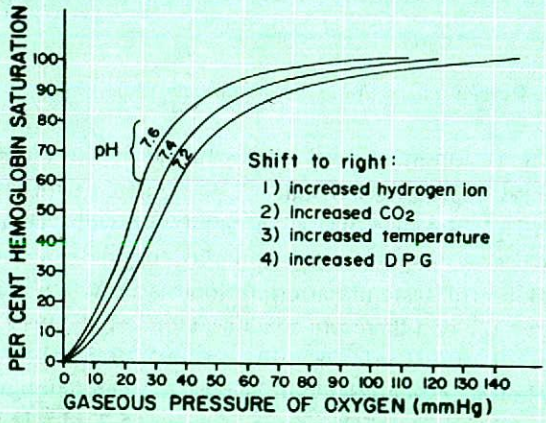


Fig. 7-9. *Shift of the oxygen-haemoglobin dissociation curve to the right by increasing -(i) H^+ (ii) CO_2 (iii) temparature (iv) 2,3-DPG.*

Factors affecting the concentration of 2,3-DPG in the red cells include p^H. Because acidosis inhibits red cell glycolysis. The 2,3-DPG concentration falls when the pH is low. Thyroid hormones, growth hormones, and androgens increase the concentration of 2,3-DPG and the P_{50}.

Exercise has been reported to produce an increase in 2,3-DPG within 60 minutes, although the rise may not occur in trained athlets. The P_{50} is also increased during exercise, because the temperature rises in active tissues and CO_2 & metabolites accumulate, lowering the pH. In addition much more O_2 is removed from each unit of blood flowing through active tissues because the tissues Po_2 declines. Finally, at low Po_2 values, the oxygen-hemoglobin dissociation curve is steep, and large amounts of O_2 are liberated per unit drop in Po_2.

Ascent to high altitude triggers a substantial rise in 2,3-DPG concentration in red cells, with a consequent increase in P_{50} and increase in the availability of O_2 to the tissues. The rise in 2,3-DPG which has a half-life of 6 hours, is secondary to the rise in blood pH. 2,3-DPG levels drop to normal upon return to sea level.

4. *CO_2 & Hydrogen ions :* Changes in the blood CO_2 & H^+ has very significant effect in enhancing oxygenation of the blood in the lung and then again in enhancing release of O_2 from the blood in the tissue. The P^H of blood falls as its CO_2 content increases, so that when the PCO_2 rises, the curve shifts to the right.

Most of the unsaturation of hemoglobin that occurs in the tissues is secondary to the decline in the PO_2, but an extra 1-2% unsaturation is due to the rise in PCO_2 and consequent shift of the dissociation curve to the right.

A convenient index of such shifts is the P_{50}, the PO_2 at which hemoglobin is half saturated with O_2. The higher the P_{50}, the lower the affinity of hemoglobin for O_2.

5. *Fetal hemoglobin* : The greater affinity of fetal hemoglobin than adult hemoglobin for O_2 fascilitates the movement of O_2 from the mother to the fetus. The cause of this greater affinity is the poor binding of 2,3-DPG by the gama polypeptide chains that replace beta chains in fetal hemoglobin.

(Ref. Ganong 22th edition, Page-667, 668)

N.B.

Red cell 2,3-DPG concentration is increased in anemia and in a variety of diseases in which there is chronic hypoxia. This fascilitates the delivary of O_2 to the tissues by raising the PO_2 at which O_2 is released in peripheral capillaries.

In blood bank, blood that is stored, the 2,3-DPG level falls and the ability of this blood to release O_2 to the tissues is reduced. This decrease, which obviously limits the benefit of the blood if it is transfused into a hypoxic patient, is less if the blood is stored in citrate-phosphate dextrose solution rather than the usual acid citrate dextrose solution.

(Ref. Ganong 22th edition, Page-669)

Shape of O_2-Hb dissociation curve :

The shape of the O_2-Hb dissociation curve is sigmoid shape. It is due to shifting affinity of the haem moiety of haemoglobin which is explained as follows- combination of the first haem with O_2 increases the affinity of the second haem for O_2, which increases the affinity of the 3rd and so forth. Oxygenation of Hb causes the two beta chains of the globin move closer together, when O_2 is given up, they move apart. This shift of beta chain is essential for the shifting affinity of haem for O_2.

(Ref. Ganong 22th edition, Page-669)

Importance of shape of O_2-Hb curve : Sigmoid shape of O_2-Hb

dissociation curve helps in quick saturation of Hb with oxygen in the lungs and binding with CO_2 in the tissue.

Function of hemoglobin : Hemoglobin has four functions-

i. It facilitates O_2 transport.
ii. It facilitates CO_2 transport.
i. It has an important role as a buffer.
i. It transports NO.

(Ref. Ganong 22th edition, Page-669)

Factors shifting the curve :

a. *Factor shifting the curve to the right :*
   i. Decreased pH (increase H^+ concentration)
   ii. Increased temperature.
   iii. Increased 2,3-diphosphoglycerate (DPG)
   iv. Increased $H^+$and increased CO_2

b. *Factors shifting to the left :*
   i. Foetal haemoglobin.
   ii. Increased p^H or decrease H^+
   iii. Decreased temperature.
   iv. Decreased PCO_2.

Reaction of Hemoglobin & Oxygen :

The dynamics of the reaction of hemoglobin with O_2 make it a particularly suitable O_2 carrier. Hemoglobin is a protein made up of sub-units each of which con-tains a haeme moiety. Haeme is a complex made up of a porphyrin and 1 atom of ferrous iron. Each of the 4 iron atoms can bind reversibly with one O_2 molecule. Since it contains 4Hb unit, the hemoglobin molecule can also be represented as Hb_4 and it actually reacts with 4 molecule of O_2 to form Hb_4O_8.

$$Hb_4 + O_2 = Hb_4O_2$$

$$Hb_4O_4 + O_2 = Hb_4O_6$$

$$Hb_4O_2 + O_2 = Hb_4O_4$$

$$Hb_4O_6 + O_2 = Hb_4O_8$$

(Ref. Ganong 22th edition, Page-666)

Difference between oxygenation and oxidation.

Oxygenation	*Oxidation*
1. No change of valency.	1. Change of valency.
2. Loose combination of O_2 occur.	2. Firm combination of O_2 occur.
3. Combination of O_2 is reversible.	3. Combination is irreversible.
4. It is temporary (transient).	4. It is permanent.

Utilization co-efficient : The percentage of blood that gives up its O_2 as it passes through the tissue capillaries is called utilization co-efficient. The normal value is about 25%.

(Ref. Guyton & Hall-11th edition, page 507).

Effect of hemoglobin to 'buffer' the tissue PO_2

(O_2 buffering action of Hb) :

Although hemoglobin is necessary for transport of O_2 to the tissue, it performs still another major function essential for life. This is its function as a "tissue oxygen buffer" system. That is the hemoglobin in the blood is mainly responsible for stabilizing the oxygen pressure in the tissues. This can be explained as follows :

1. ***Role of hemoglobin in maintaining constant PO_2 in the tissues*** : Under basal conditions the tissue require about 5 milliliters of oxygen from each deciliter (100ml) of blood passing through the tissue capillary. Again when 15 milliliters of oxygen is released, the PO_2 must fall to about 40 mm Hg. Therefore the tissue PO_2 normally can not rise above this 40 mm Hg level, for it such should occur; the oxygen needed by the tissue could not be released from the hemoglobin. In this way the hemoglobin nomally sets an upper limit on the gaseous pressure in the tissues at appro ximately 40 mm Hg.

   On the other hand, In heavy exercise extra large amounts of O_2 must be delivered from the hemoglobin to the tissue this can be achieved with very little furthur decrease in tissue PO_2 , that is a small fall in PO_2 causes large amount of O_2 to be released.

2. ***Value of hemoglobin for maintaining constant tissue PO_2 when atmospheric oxygen concentration changes markedly*** : The normal PO_2 in the alveoli is approximately 104 mm Hg. but as one ascends a mountain or ascends in a air plane, the PO_2 can easily fall to less than half this. *Or* when one enters areas of compressed air such as deep in the sea or in pressurized chambers, the PO_2 may rise to ten times this level. Even so, the tissue PO_2 changes very little.

   Let us explain - When the alveolar PO_2 is decreased to as low as 60 mm Hg, the arterial Hb is still 89% staturated, only 8% below the normal saturation of 97%. Further more, the tissues still remove approxi-mately 5 milliliters of O_2 from each deciliter of blood passing through the tissues, to remove this O_2, the PO_2 venous blood falls to 35 mm Hg, only 5 mm below the normal value. Thus the tissue PO_2 hardly changes, despite the marked fall in alveolar PO_2 from 104 to 60 mm Hg.

   On the other hand, when alveolar PO_2 rises as high as 500 mm Hg, the maximum oxygen saturation of Hb can never rise above 100%, which is only 3% above the normal level of 97%. Then when the blood passes through the tissue capillaries, it still loses several milliliters of O_2 to the tissues, which automatically reduces the Po_2 of the capillary blood to a value only a few millimeters greater than the normal 40 mm Hg.

Therefore, the level of alveolar O_2 may vary greatly from 60 to more than 500 mm of Hg Po_2 and still the Po_2 in the tissue does not vary more than a few millimeters from normal illustrating beautifully the tissue oxygen buffer function of the blood Hb.

(Ref. Guyton & Hall-11th edition, page 507)

N.B.

* 1 gm pure Hb contains 1.39 ml of O_2
* 1 gm impure Hb contains 1.34 ml of O_2
* 100 ml of arterial blood contains 19.8 ml of O_2
* 100 ml of venous blood contains 15.2 ml of O_2.

(Ref Ganong 22th edition, Page 667)

Formation and catabolism of 2, 3-BPG :

Glucose 6-PO_4
↓
3-Phosphoglyceraldehyde
↓
1,3-Biphosphoglycerate
2,3-BPG mutase →
Phospho glycerate kinase ↓
2,3-Biphosphoglycerat (2,3-BPG)
2,3-BPG phosphatase →
3-phosphoglycerate
↓
Pyruvate.

(Ref. Ganong 22th edition; page 668)

Transport of CO_2

CO_2 is continually produce in the tissue cells due to metabolic activity and this increases the intracellular Pco_2. So, CO_2 is released from the cell in the blood.

1. *Diffusion of CO_2 from cell into interstitial fluid :* Intracellular Pco_2 is about 46 mm of Hg. Interstitial fluid

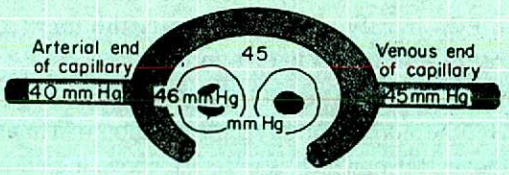


Fig. 7-10. *Uptake of CO_2 by the blood in the capillaries.*

Pco_2 is about 45 mm of Hg. Thus pressure difference is 1 mm of Hg that causes CO_2 to diffuse into interstitial fluid .

2. *Diffusion of CO_2 from interstitial fluid to blood :* Interstitial fluid Pco_2 about 45 mm of Hg . Arterial blood entering the tissue capillary Pco_2 is 40 mm of Hg. So, CO_2 diffuses into blood from interstitial fluid.

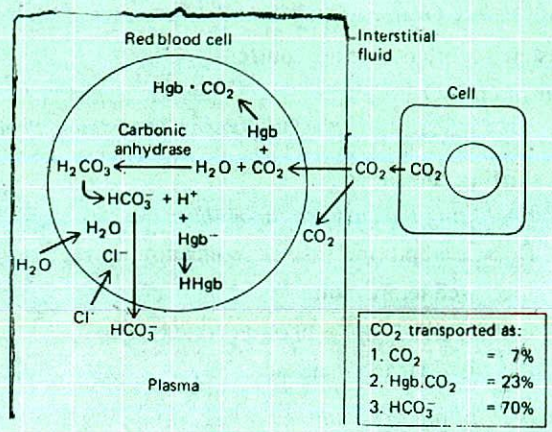


Fig. 7-11. *Transport of CO_2 in the blood.*

3. *Transport of CO_2 in the blood :* In blood CO_2 is transported in three form :
   i. In dissolved state : 7 %
   ii. In the form of HCO_3 and H^+ : 70 %
   iii. In combination with Hb : 23 %.

   i. *Transport of CO_2 in dissolved state :* The Pco_2 in venous blood is 45 mm of Hg and the amount of CO_2 dissolved in the fluid at 45 mm of Hg is about 2.7 ml per dL of blood.

   The CO_2 in arterial blood is 40 mm of Hg and the amount of CO_2 dissolved at 40 mm of Hg. is about 2.4 ml per dl. Therefore only, 0.3 ml (2.7-2.4) of CO_2 is transported in the form of dissolved state per dL of blood

   ii. *Transport of CO_2 in the form of HCO_3^- :* The dissolved CO_2 in the blood reacts with water catalyzes by carbonic anhydrase to form carbonic acid which inturn dissociate into HCO_3^- and H^+. Most of the H^+ then combine with Hb buffer system. Then almost all the HCO_3^- diffuses by the chloride shift mechan ism and this made possible by the presence of biocarbonate-chloride carrier protein in the membrane of the red cells.

   iii. *Transport of CO_2 as carbamino-haemoglobin or combination with Hb :* CO_2 also combine with haemoglobin to form carbaminohaemoglobin ($Hbco_2$) by very loose bond. So that CO_2 easily released into the alveoli where the Pco_2 is lower than tissue.

   A small amount of CO_2 also combine with plasma protein and transport in the same way.

4. *Diffusion of CO_2 from blood into alveoli of lung :* Pco_2 of

venous blood entering the lungs is 45 mm of Hg. Pco_2 of alveolar air is 40 mm of Hg. So the required amount of CO_2 diffuses out of pulmonary capillary into the alveoli and then into the atmosphere.

(Ref. Guyton & Hall-11th Edition, page 510, 511)

Chemical forms in which CO_2 is carried to the blood

In the form of chemical compound CO_2 is transported in two different ways :

1. As bicarbonate ions
2. As carbamino compound.
   a. Carbamino-hemoglobin.
   b. Carbamino-protein.

1. ***As bicarbonate ion*** :
   a. *In RBC :* The dissolve CO_2 in the blood reacts with water to form carbonic acid, catalized by an enzyme, carbonicanhydrase, accelerating the reaction about 5000 fold.

$$CO_2 + H_2O \xrightarrow{\text{Carbonic anhydrase}} H_2CO_3$$

As soon as carbonic acid is form in the red cells, dissociates into H^+ and HCO_3^-

$$H_2CO_3 \longrightarrow H^+ + HCO_3^-$$

Most of the H^+ then combine with Hb in the red blood cells, because Hb is a powerful acid base buffer.

$$H^+ + Hb \longrightarrow HbH^+$$

As the formation of HCO_3^- in RBC is much more rapid than plasma, the cell become alkaline and HCO_3 diffuses into the plasma, while choloride ions diffuse into the cells to take their place.

   b. *In plasma :*
      i. With the plasma proteins .

$$NaPr + H_2CO_3 = HPr + NaHCO_3$$

      ii. With phosphates -

$$Na_2HPO_4 + H_2CO_3 = NaHCO_3 + NaH_2PO_4$$

2. *As carbamino compound* :
   a. Carbamino-hemoglobin: CO_2 combines with- NH_2 group of globin part of hemoglobin to form carbamino hemoglobin.

$$CO_2 + HbNH_2 \longrightarrow HbNHCOOH.$$

   b. Carbamino-protein: In combination with plasma protein form carbamino - protein.

$$PrNH_2 + CO_2 = PrNHCOOH.$$

In these chemical form CO_2 is transported.

(Ref. Guyton & Hall-11th edition & others)

Fate of CO_2 in blood

A. *In plasma* :
   1. Dissolved
   2. Formation of carbamino compounds with plasma protein
   3. Hydration, H^+ buffered, HCO_3^- in plasma.

B. *In red blood cells* :
   1. Dissolved
   2. Formation of carbamino hemoglobin
   3. Hydration, H^+ buffered, 70% of HCO_3^- enters the plasma.
   4. Cl^- shifts into cells, mosm in cells increases.

(Ref. Ganong 22th edition, Page 670)

Summary of CO_2 transport :

1. *Each deciliter (100ml) of arterial blood contains 49 ml of CO_2.*
   a. Dissolved state : 2.6 mL
   b. Carbamino compounds : 2.6 mL
   c. As HCO_3^- : 43.8 mL
2. *In the tissues, 3.7 mL of CO_2 per deciliter (100mL) of blood is added.*:
   a. Stays in dissoved state : 0.4 ml
   b. Forms carbamino compound : 0.8 ml
   c. Forms HCO_3^- : 2.5 ml.
3. *The pH of the blood drops from 7.40 to 7.36.*
4. *Each deciliter (100ml) of venous blood contains (49 + 3.7) 52.7 ml of CO_2 :*
   a. Dissolved state : (2.6 + 0.4) 3.0 ml
   b. Carbamino compounds : (2.6 + 0.8) 3.4 ml
   c. As HCO_3^- : (43.8 + 2.5) 46.3 ml.
5. *In the lungs, the processes are reversed, and the 3.7 ml of CO_2 is discharged into the alveoli.*
6. About 200 ml ($\frac{3.7 \times 5500}{100}$ Here, cardiac output =5500 ml) of CO_2 per minute at rest and much larger amounts during exercise are transported from tissues to the lungs and exereted.

(Ref. Ganong 22th edition, Page-670)

Chloride shift mechanism

As a result of ionic imbalance due to more HCO_3^- formation in the red blood cells, they pass out of the red cells to the plasma and inturns Cl^- passes into the red cells from plasma. This phenomenon is called chloride shift or Hamburger shift.

CO_2 on entering into RBC binds with water and form carbonic acid which inturn with the help of carbonic anhydrase dissociates into hydrogen ion and bicarbonate ion (*Fig. 7-13*). The H^+ binds with the buffer system of haemoglobin. The

bicarbonate ion then increases the alkalinity of RBC. To correct this alkalinity of red blood cells bicarbonate ions diffuses into the plasma while chloride from plasma enters into red blood cells to take their place.

(Ref. Ganong 22th edition, Page-670 & Guyton 11th)

N.B. Note that for each CO_2 molecule added to a red cell, there is an increase of one osmotically active particle- either an HCO_3^- or a Cl^- in the red cell. Consequently, the red cells take up water and increase in size. For this reason, plus the fact that a small amount of fluid in the arterial blood returns via the lymphatics rather than the veins, the hematocrit of venous blood is normally 3% greater than that of the arterial blood. In the lungs the Cl^- moves out of the cells and they shrink.

(Ref. Ganong 22th edition, Page-670 & Guyton 11th)

Gas content of blood

ml/dl of blood containing 15 gm of haemoglobin

Gas	Arterial blood ($PO_2$95 mm Hg; PCO_2 40 mm Hg; Hb 97% saturated)		Venous blood (PO_2 40 mm Hg; PO_2 46 mm Hg; Hb 75% saturated)	
	Dissolved	Combined	Dissolved	Combined
O_2	0.29	19.5	0.12	15.1
CO_2	2.62	46.4	2.98	49.7
N_2	0.98	0	0.98	0

(Ref. Ganong 22th edition, Page-667)

Bohr Effect

Shift of oxygen-haemoglobin dissociation curve in response to changes in the blood carbon dioxide and hydrogen ions has a significant effect in enhancing oxygenation of blood in the lungs and then again in enhancing release of oxygen from the blood in the tissues. This is called Bohr effect.

It can be explained as follws : As the blood passes through the lungs, carbon dioxide diffuses from the blood into the alveoli. This reduces the blood PCO_2 and decreases the hydrogen ion concentration because of the resulting decrease in blood carbonic acid. Both these effects shift the oxygen-haemoglobin dissociation curve to the left and upwards. Therefore the quantity of oxygen that binds with the hemoglobin at any given alveolar PO_2 becomes considerably increased, thus allowing greater oxygen transport to the tissues.

Then when the blood reaches the tissue capillaries, exactly the opposite effects occur. Carbondioxide entering the blood from tissues shifts the curve to the right-ward, which displaces oxygen from the haemoglobin and therefore delivers oxygen to the tissues at a higher PO_2 than would otherwise occur.

(Ref. Guyton & Hall-11th edition, page 508)

Haldane Effect

Binding of oxygen with haemoglobin tends to displace carbon dioxide from blood, this effect is called the *Haldane effect*. It is important in promoting carbon dioxide transport.

The Haldane effect results from the simple fact that combination of oxygen with hemoglobin in the lungs causes the hemoglobin to become a stronger acid. This inturn displaces carbon dioxide from the blood and into the alveoli in two ways :

i. The more highly acidic hemoglobin has less tendency to combine with carbon dioxide to formcarbaminohemoglobin, thus displacing much much of the carbon dioxide that is present in the carbamino form from the blood.

ii. The increased acidity of the hemoglobin also causes it to release excess of hydrogen ions, and these in turn bind with bicarbonate ions to form carbonic acid; then this dissociates into carbon dioxide and water, and carbon dioxide is released from the blood into the alveoli.

In the tissue capillaries, the Haldane effect causes increased pickup of carbon dioxide because of oxygen removal from the hemoglobin, and in the lungs, it causes increased release of carbon dioxide because of oxygen pickup by the hemoglobin.

(Ref. Guyton & Hall-11th edition, page 511)

Control of Ventilation

Respiration is so adjusted that it keeps our bodily oxygen need satisfied, drives out carbon dioxide and hydrogen ions, yet it operates at low cost. Further, repiration can take care of the changes of our body needs by altering the frequency (normally about 14/min) and depth (normally 500 ml) of individual excursions and do that automatically. Further, respiratory movements are automatic and rhythmic.

These features, viz, automaticity, rhythmicity and adjustibility to the needs are dependent on the presence of a respiratory center (RC) which receives many feed backs from various parts of the body to adjust according to the needs.

The respiratory center consists of-

i. Medullary (DRG & VRG)
   a. Dorsal respiratory group (DRG)
   b. Ventral respiratory group (VRG)

ii. Pontine (apneustic and pneumotaxic) centers.

Inspiratory neurons, mostly in the DRG are always active, only the activity regularly increases and decreases. When it increases, the RC center discharges- inspiration begins. When decreases, the inspiration stops → expiration begins.

The inspiratory neurons are strongly influenced by reflexes (eg, load detecting reflex /Hering breuer reflex and so on), $PaCO_2$ and so on.

$PaCO_2$ acts mostly via central chemoreceptors (CC) of medulla. At exceptional times, depression of PaO_2 becomes an important (carotid and aortic bodies).

Finally, sometimes, higher centers (cortex/hypo thalamus) appear in the picture of control.

Cause of rhythmicity is rather speculative.

Breath Holding

Respiration can be voluntarily inhibited for some time, but eventually the voluntary control is overridden. *The point at which breathing can no longer be voluntarily inhibited is called the* ***breaking point***.

Breaking is due to the rise in arterial P_{CO_2}, and the fall in P_{O_2}. Individuals can hold their breath longer after removal of the carotid bodies.

Breathing 100% oxygen before breath holding raises alveolar P_{O_2} initially, so that the breaking point is delayed. The same is true of hyperventilating room air, because CO_2, is blown off and arterial P_{CO_2} is lower at the start.

Reflex or mechanical factors appear to influence the breaking point, since subjects who hold their breath as long as possible and then breathe a gas mixture low in O_2 and high in CO_2 can hold their breath for an additional 20 seconds or more.

Psychological factors also play a role, and subjects can hold their breath longer when they are told their performance is very good than they are not.

(Ref. Ganong 22th edition, Page 677)

Regulation of respiration

Spontaneous respiration is produced by rhythmic discharge of motor neurons that innervate the respiratory muscles. This discharge is totally dependent on nerve impulses from the brain; breathing stops if the spinal cord is transected above the origin of the phrenic nerves.

The rhythmic discharges from the brain that produce spontaneous respiration are regulated by alternations in arterial P_{O_2}, P_{CO_2} and H^+ concentration, and this chemical control of breathing is supplemented by a number of nonchemical influences.

(Ref. Ganong 22th edition, Page 671)

Respiratory centre

The respiratory center is composed of several groups of neurons located bilaterally in the medulla oblongata and pons. It is divided into three major collections of neurons :

i. *Dorsal respiratory group*, located in the dorsal portion of the medulla, which mainly causes inspiration.

ii. *Ventral respiratory group*, located in the ventrolateral part of the medulla, which can cause either expiration or inspiration, depending on which neurons in the group are stimulated.

iii. *Pneumotaxic center*, located dorsally in the superior portion of the pons, which helps control the rate and pattern of breathing.

The dorsal respiratory group of neurons plays the most fundamental role in the control of respiration.

(Ref. Guyton & HAll-11th Edition, page 514)

A. ***Dorsal respiratory group*** *(Inspiratory centre)* : The dorsal respiratory group of neurons extends most of the length of the medulla. All or most of its neurons are located within the *nucleus of the tractus solitarius*, although additional neurons in the adjacent reticular substance of the medulla also play important roles in respiratory control.

The *nucleus of the tractus solitarius* is the sensory termination of both the vagal and the glossopharyngeal nerves, which transmit sensory signals into the respiratory center :

1. from the peripheral chemoreceptors
2. from the baroreceptors
3. from several types of receptors in the lung.

All the signals from these peripheral areas help to control respiration.

Function : The basic rhythm of respiration is generated mainly in the dorsal respiratory group of neurons.

(Ref. Guyton & Hall-11th Edition, page 514)

B. ***Ventral respiratory group*** *(Functions in both inspiration and expiration)* : Located in each side of the medulla, about 5 millimeters anterior and lateral to the dorsal respiratory group of neurons, is the ventral respiratory group or neurons, found in the nucleus ambiguus rostrally and the nucleus retroambiguus caudally. The function of this neuronal group differs from that of the dorsal respiratory group in several important ways :

1. The neurons of the ventral respiratory group remain almost totally *inactive* during normal quiet respiration. Therefore, normal quiet breathing is caused only by repetitive inspiratory signals from the dorsal respiratory group transmitted mainly to the diaphragm, and expiration results from elastic recoil of the lungs and thoracic cage.
2. There is no evidence that the ventral respiratory neurons participate in the basic rhythmical oscillation that controls respiration.
3. When the respiratory drive for increased pulmonary ventilation becomes greater than normal, respiratory signals spill over into the ventral respiratory neurons from the basic oscillating mechanism of the dorsal respiratory area. As a consequence, the ventral respiratory area does then contribute its share to the respiratory drive as well.

4. Electrical stimulation of some of the neurons in the ventral group causes inspiration, whereas stimulation of others causes expiration. Therefore, these neurons contribute to both *inspiration* and *expiration*. They are especially important in providing the powerful expiratory signals to the abdominal muscles during very heavy expiration. Thus, this area operates more or less as an overdrive mechanism when high levels of pulmonary ventilation are required, especially during exercise.

(Ref. Guyton & HAll-11th Edition, page 515)

C. ***Pneumotaxic centre*** : The pneumotaxic center, located dorsally in the nucleus parabrachialis of the upper pons, transmits signals to the inspiratory area. The primary effect of this center is to control the "*switch-off*" point of the inspiratory ramp, thus controlling the duration of the filling phase of the lung cycle. When the pneumotaxic signal is strong, inspiration might last for as little as 0.5 second, thus filling the lungs only slightly; but when the pneumotaxic signals are weak, inspiration might continue for 5 or more seconds, thus filling the lungs with a great excess of air.

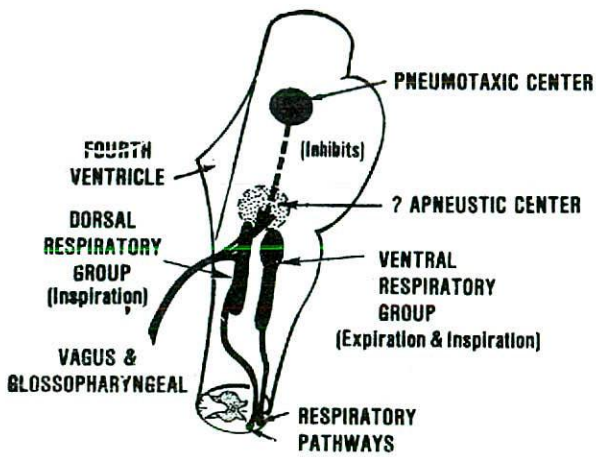


Fig. 7-12. *Location of Respiratory centre.*

Function : The function of the pneumotaxic center is primarily to limit inspiration. This has a secondary effect of increasing the rate of breathing, because limitation of inspiration also shortens expiration and the entire period of respiration. A strong pneumotaxic signal can increase the rate of breathing to 30 to 40 breaths per minute, whereas a weak pneumotaxic signal may reduce the rate to only 3 to 5 breaths per minute.

(Ref. Guyton & HAll-11th Edition, page 515)

D. ***Apneustic centre :*** To add confusion to our knowledge about respiratory center function, there is another strange center in the lower part of the pons called the apneustic center.

Function : Under a few conditions, this center sends signals to the dorsal respiratory group of neurons to prevent or retard the "switch-off" of the inspiratory ramp signal. Therefore, the lungs become almost completely filled with air, and only occasional short expiratory gasps occur.

The value of the apneustic center is not understood, but it presumably operates in association with the pneumotaxic center to control the intensity of inspiration.

(Ref. Guyton & HAll-10th Edition, page 475)

Airway and lung receptors

Vagal innervation :

i. *Myelinated fibers* :

Type	*Location in Interstitium*	*Stimulus*	*Response*
Slowly adapting	Among airway smooth muscle cells(?)	Lung inflation	Inspiratory time shortening Hering-Breuer inflation and deflation reflexes Bronchodilation Tachycardia
Rapidly adapting	Among airway epithelial cells	Lung hyperinflation Exogenous and endogenous substances (eg, histamine, prostaglandins)	Hyperpnea Cough Bronchoconstriction Mucus secretion

ii. *Unmyelinated C fibers* :

Type	*Location in Interstitium*	*Stimulus*	*Response*
Pulmonary C fibers	Close to blood vessels	Lung hyperinflation Exogenous and endogenous substances (eg, capsaicin, bradykinin, serotonin)	Apnea followed by rapid breathing Bronchoconstriction Bradycardia Hypotension Mucus secretion.

(Ref. Ganong 22th Edition; page 679)

Responses mediated by receptors in the airway and lungs :

Receptors in the airways and lungs are innervated by myelinated and unmyelinated vagal fibers. The unmyelinated fibers are C fibers. The receptors innervated by myelinated fibers are commonly divided into ***slowly adapting receptors*** and ***rapidly adapting receptors*** on the basis of whether sustained stimulation leads to prolonged or transient discharge in their afferent nerve fibers. The other group of receptors presumably consists of the endings of C fibers, and they are divided into pulmonary and bronchial subgroups on the basis of their location.

The shortening of inspiration produced by vagal afferent activity is mediated by slowly adapting receptors. So are the *Hering-Breuer reflexes.*

Hering-Breuer inflation reflex is an increase in the duration of expiration produced by steady lung inflation and *Hering-Breuer deflation reflex*1st is a decrease in the duration of expiration

produced by marked deflation of the lung. Because the rapidly adapting receptors are stimulated by chemicals such as histamine, they have been called ***irritant receptors***. Activation of rapidly adapting receptors in the trachea causes coughing, bronchoconstriction and mucus secretion, and activation of rapidly adapting receptors in the lung may produce hyperpnea.

Because the C fiber endings are close to pulmonary vessels, they have been called ***J*** *(juxtacapillary)* ***receptors***. They are stimulated by hyperinflation of the lung but they respond as well to intravenous or intracardiac administration of chemicals such as capsaicin. The reflex response that is produced is apnea followed by bradycardia, and hypotension (pulmonary reflex). A similar response is produced by receptors in the heart (Bezold-Jarisch reflex or the coronary chemoreflex). The physiologic role of this reflex is uncertain, but it probably occurs in pathologic states such as pulmonary congestion or embolization, in which it is produced by endogenously released substances. *(Q. Write short notes on J receptors)*

(Ref. Ganong 22th Edition; page 678)

Regulation of respiration

Respiration is regulated by the following ways :

1. *Nervous control of breathing*
   i. Voluntary control
   ii. Automatic control.
2. *Chemical control of respiration* :
   a. Direct chemical control of respiration affecting the respiratory centre by-
      i. Carbondioxide (PCO_2)
      ii. Hydrogen ions (H^+).
   b. Peripheral chemoreceptor system for control of respiratory activity-
      i. Role of oxygen
      ii. Role carbon dioxide
      ii. Role hydrogen ions.
3. *Non chemical influences on respiration* (other effects that affect respiration) :
   a. Responses mediated by receptors in the airways and lungs.
   b. Coughing and sneezing
   c. Responses in patients with heart-lung transplants
   d. Afferents from 'higher centers'
   e. Afferents from proprioceptors
   f. Respiratory components of visceral reflexes
   g. Respiratory effects of baroreceptor stimulation
   h. Effects of sleep.
4. *Hormonal effects on respiration.*

(Ref. Ganong 22th Edition & Guyton 11th Edition)

1. **Nervous control of breathing** : Two separate neural mechanisms regulate respiration. One is responsible for vlountary control and the other for automatic control. The voluntary system is located in the cerebral cortex and sends impulses to the respiratory motor neurons via corticospinal tracts. The automatic system is located in the pons and medulla, & the efferent output from this system to the respiratory motor neurons is located in the white matter of the spinal cord between the lateral and ventral corticospinal tracts. The nerve fibers mediating inspiration converge on the phrenic motor neurons located in the ventral horns from C_3 to C_5 and the external intercostal motor neurons in the ventral horns throughout the thoracic cord. The fibers concerned with the expiration converge primarily on the internal intercostal motor neurons in the thoracic cord.

   The motor neurons to the expiratory muscles are inhibited when those supplying the inspiratory muscles are active, and vice versa. *(Ref. Ganong 22th edition, Page-671)*

Rhythmic breathing *(Nervous regulation)* : Rhythmic breathing means normally inhaling and exhaling of air at a regular interval of time. The rhythmic breathing is controlled by the respiratory centres which are located in the grey mater of the pons and medulla of brain stem.

Mechanism of control : At first apneustic centre is stimulated either by excess Pco_2 in body fluid or by the stretch receptors of lungs and discharge stimulatory impulse to the inspiratory centre and slightly inhibitory impulse to the expiratory centre. The stimulated inspiratory centre then discharge stimulatory impulse to the diaphragm and the external intercostal muscle through 3rd, 4th and 5th cervical nerve and anterior horn cell of thoracic spinal nerve which causes contraction of the diaphragm and intercostal muscles.

By the action of the diaphragm and the intercostal muscles lungs expand and inspiration takes place. In normal respiration, it begins weakly and increases steadily in a ramp manner for about 2 seconds. Then it ceases abruptly for approximately the next 3 seconds, which turns off the excitation of the diaphragm and allows elastic recoil of the lungs and the chest wall to cause expiration.

When inspiration occurs, the stretch receptors which are present in the wall of the alveoli of lung stimulated, send inhibitory impulses through the vagus nerve to the apneustic centre. In the same time the pneumotaxic centre discharge inhibitory impulse to the apneustic centre and stimulatory impulse to the expiratory centre. As a result the apneustic centre ceases its activity and expiration takes place.

As a result of expiration the lungs contracts. So stretch receptor does not send impulse to apneustic centre and again inspiration takes place. By this process normal rhythmic breathing is regulated.

(Ref. Ganong 22th Edition & Guyton 11th Edition)

Hearing breuer inflation reflex : In addition to the neural

respiratory control mechanisms operating entirely within the brain stem, sensory nerve signals from the lungs also help to control respiration. Most important, located in the muscular portions of the walls of the bronchi and bronchioles throughout the lungs are stretch receptors that transmit signals through the vagi into the dorsal respiratory group of neurons when the lungs become overstretched. These signals affect inspiration in much the same way as signals from the pneumotaxic center; that is, when the lungs become overly inflated, the stretch receptors activate an appropriate feedback response that "switches off" the inspiratory ramp and thus stops further inspiration. This is called the *Hering-Breuer inflation reflex*. This reflex also increases the rate of respiration, the same as is true for signals from the pneumotaxic center.

In human beings, the Hering-Breuer reflex probably is not activated until the tidal volume increases to greater than about 1.5 liters. Therefore, this reflex appears to be mainly a protective mechanism for preventing excess lung inflation rather than an important ingredient in the normal control of ventilation.

(Ref. Guyton & Hall-11th Edition; Page 516)

2. **Chemical regulation** : The ultimate goal of respiration is to maintain proper concentrations of oxygen, carbon dioxide, and hydrogen ions in the tissues. It is fortunate, therefore, that respiratory activity is highly responsive to changes in each of these.

   a. *Excess carbon dioxide or excess hydrogen ions* in the blood mainly act directly on the *respiratory center* itself, causing greatly increased strength of both the inspiratory and the expiratory motor signals to the respiratory muscles.

   b. *Oxygen*, in contrast, does not have a significant direct effect on the respiratory center of the brain in controlling respiration. Instead, it acts almost entirely on *peripheral chemooreceptors* located in the carotid and aortic bodies, and these in turn transmit appropriate nervous signals to the respiratory center for control of respiration.

   a. ***Direct chemical control of respiratory center activity by carbon dioxide and hydrogen ions*** *(chemosensitive area of the respiratory center)* : There are three areas of the respiratory center- the dorsal respiratory group of neurons, the ventral respiratory group, and the pneumotaxic center. It is believed that none of these are affected directly by changes in blood carbon dioxide concentration or hydrogen ion concentration. Instead, an additional neuronal area, a sensitive chemosensative area, is located bilaterally lying only one-fifth millimeter beneath the ventral surface of the medulla. This area is highly sensitive to changes in either blood Pco_2, or hydrogen ion concentration, and it in turn excites the other portions of the respiratory center.

(Ref. Guyton & Hall-11th Edition; Page 516)

i. ***Response of the chemosensitive neurons to Hydrogen ions****- probably the primary stimulus* : The sensory neurons in the chemosensitive area are especially excited by hydrogen ions; in fact, it is believed that hydrogen ions are perhaps the only important direct stimulus for these neurons. However, hydrogen ions do not easily cross the blood brain barrier. For this reason, changes in hydrogen ion concentration in the blood have considerably less effect in stimulating the chemosensitive neurons than do changes in blood carbon dioxide, even though carbon dioxide is believed to stimulate these neurons secondarily by changing the hydrogen ion concentration.

(Ref. Guyton & Hall-11th Edition; Page 516)

ii. ***Effect of blood carbon dioxide*** *to stimulate the chemo sensitive area* : Although carbon dioxide has little direct effect in stimulating the neurons in the chemosensitive area, it does have a potent indirect effect. It does this by reacting with the water of the tissues to form carbonic acid. This in turn dissociates into hydrogen and bicarbonate ions; the hydrogen ions then have a potent direct stimulatory effect.

Why does blood carbon dioxide have a more potent effect in stimulating the chemosensitive neurons than do blood hydrogen ions? The answer is that the blood-brain barrier is almost completely impermeable to hydrogen ions, but carbon dioxide passes through this barrier almost as if the barrier did not exist. Consequently, whenever the blood Pco_2 increases, so does the Pco_2 of both the interstitial fluid of the medulla and the cerebrospinal fluid. In both these fluids, the carbon dioxide immediately reacts with the water to form hydrogen ions. Thus, paradoxically, more hydrogen ions are released into the respiratory chemosensitive sensory area when the blood carbon dioxide concentration increases than when the blood hydrogen ion concentration increases. For this reason, respiratory center activity is increased very strongly by changes in blood carbon dioxide, a fact that we subsequently discuss quantitatively.

Decreased stimulatory effect of carbon dioxide after the first 1 to 2 Days *:* Excitation of the respiratory center by carbon dioxide is great the first few hours after the carbon dioxide first increases but then gradually declines over the next 1 to 2 days, decreasing to about one fifth the initial effect. Part of this decline results from renal readjustment of the hydrogen ion

concentration back toward normal after the carbon dioxide first increases the hydrogen concentration. The kidneys achieve this by increasing the blood bicarbonate, which then binds with the hydrogen ions in the blood and cerebrospinal fluid to reduce their concentrations. But even more important, over a period of hours, the bicarbonate ions also slowly diffuse through the *blood-brain* and *blood-cerebrospinal fluid barriers* and combine directly with the hydrogen ions around the respiratory neurons as well, thus reducing the hydrogen ions back to near normal.

Therefore, a change in blood carbon dioxide concentration has a potent *acute effect* on controlling respiratory drive but only a weak *chronic effect* after a few days' adaptation.

(Ref. Guyton & Hall-11th Edition; Page 517)

Unimportant of oxygen for direct control of respiratory center : Changes in oxygen concentration have virtually no direct effect on the respiratory center itself to alter respiratory drive (although they do have an indirect effect, acting through the peripheral chemoreceptors).

We know that *hemoglobin-oxygen buffer system* delivers almost exactly normal amounts of oxygen to the tissues even when the pulmonary Po_2 changes from a value as low as 60 mm Hg up to a value as high as 1000 mm Hg. Therefore, except under special conditions, proper delivery of oxygen can occur despite changes in lung ventilation ranging from slightly below one-half normal to as high as 20 or more times normal. This is not true for *carbon dioxide*, because both the blood and tissue Pco_2, change almost exactly inversely with the rate of pulmonary ventilation; thus, evolution has made *carbon dioxide the major controller of respiration, not oxygen.*

Yet for those special condition in which the tissues get into trouble for lack of oxygen, the body has a special mechanism for respiratory control located in the peripheral chemoreceptors, outside the brain respiratory center; this mechanism responds when the blood oxygen falls too low, mainly below a Po_2 of 70 mm Hg.

(Ref. Guyton & Hall-11th Edition; Page 517)

b. ***Peripheral chemoreceptor system for control of respiratory activity*** *(Role of oxygen in respiratory control)* : In addition to control of respiratory activity by the respiratory center itself, still another mechanism is available for controlling respiration. This is the *peripheral chemoreceptor* system. Special nervous chemical receptors, called chemoreceptors, are located in several areas outside the brain. They are espicially important for detecting changes in the blood, although they also respond to a lesser extent to change in carbon dioxide and hydrogen ion concentrations. The chemoreceptors in turn transmit nervous signals to the respiratory center in the brain to help regulate respiratory activity.

Most of the chemoreceptors are located in the *carotid bodies*. However, a sizable number are also in the *aortic bodies*, and a few are located elsewhere in association with other arteries of the thoracic and abdominal regions of the body.

The *carotid bodies* are located bilaterally in the bifurcations of the common carotid arteries, and their afferent nerve fibers pass through Hering's nerves to the glossopharyngeal nerves and then to the dorsal respiratory area of the medulla. The *aortic bodies* are located along the arch of the aorta; their afferent nerve fibers pass through the vagi also to the dorsal respiratory area.

Each of the chemoreceptor bodies receives a special blood supply through a minute artery directly from the adjacent arterial trunk. Furthermore, blood flow through these bodies is extreme, 20 times the weight of the bodies themselves each minute. Therefore, the percentage removal of oxygen from the flowing blood is virtually zero. This means that the chemoreceptors are exposed at all times to arterial blood, not venous blood, and their Po_2s are arterial Po_2s.

(Ref. Guyton & Hall-11th Edition; Page 517)

Stimulation of the chemoreceptors by decreased arterial oxygen *:* When the oxygen concentration in the arterial blood falls below normal, the chemoreceptors become strongly stimulated. The impulse rate is particularly sensitive to changes in arterial Po_2, in the range from 60 down to 30 mm Hg, a range in which hemoglobin saturation with oxygen decreases rapidly.

Basic mechanism of stimulation of the chemoreceptors by oxygen deficiency : The exact means by which low Po_2 excites the nerve endings in the carotid and aortic bodies is still unknown. However, these bodies have multiple highly characteristic glandular-like cells, called *glomus cells*, that synapse directly or indirectly with the nerve endings. Some investigators have suggested that these glomus cells might function as the chemoreceptors and then in turn stimulate the nerve endings. But other studies suggest that the nerve endings themselves are directly sensitive to the low Po_2.

(Ref. Guyton & Hall-11th Edition; Page 518)

Effect of carbon dioxide and hydrogen ion concentration on chemoreceptor activity : An increase in either carbon dioxide concentration or hydrogen ion concentration also excites the chemoreceptors and in this way indirectly increases respiratory activity. However, the direct effects of both these factors in the respiratory center itself are so much more powerful than their effects mediated through the chemoreceptors (about seven times as powerful) that for most practical purposes, the indirect effects of carbon dioxide and hydrogen ions through the chemoreceptors do not need to be considered. Yet there is *one difference between the peripheral and central effects of carbon dioxide:* the stimulation by way of the peripheral chemoreceptors occurs as much as five times as rapidly as central stimulation, so that the peripheral chemoreceptors might be especially important to increase the rapidity of response to carbon dioxide at the onset of exercise.

(Ref. Guyton & Hall-11th Edition; Page 518)

3. **Non chemical influences on respiration** *(other effects that affect respiration)* :

   a. ***Responses mediated by receptors in the airways & lungs*** : Receptors in the airways and lungs are innervated by myelinated and unmyelinated vagal fibers. The unmyelinated fibers are C fibers. The receptors innervated by myelinated fibers are commonly divided into *slowly adapting receptors* and *rapidly adapting receptors* on the basis of whether sustained stimulation leads to prolonged or transient discharge in their afferent nerve fibers. The other group of receptors presumably consists of the endings of C fibers, and they are divided into pulmonary and bronchial subgroups on the basis of their location.

   The shortening of inspiration produced by vagal afferent activity is mediated by slowly adapting receptors. So are the *Hering-Breuer reflexes*. The *Hering-Breuer inflation reflex* is an increase in the duration of expiration produced by steady lung inflation, and the *Hering-Breuer deflation reflex* is a decrease in the duration of expiration produced by marked deflation of the lung.

   Because the rapidly adapting receptors are stimulated by chemicals such as histamine, they have been called *irritant receptors*. Activation of rapidly adapting receptors in the trachea *causes coughing, bronchoconstriction, and mucus secretion*, and activation of rapidly adapting receptors in the lung may produce *hyperpnea*.

   Because the C fiber endings are close to pulmonary vessels, they have been called *J (juxtacapillary) receptors*. They are stimulated by hyperinflation of the lung, but they respond as well to intravenous or intracardiac administration of chemicals such as capsaicin. The reflex response that is produced is apnea followed by rapid breathing, bradycardia, and hypotension (*pulmonary chemoreflex*). A similar response is produced by receptors in the heart (*Bezold-Jarisch reflex or the coronary chemoreflex*). The physiologic role of this reflex is uncertain, hut it probably occurs in pathologic states such as pulmonary congestion or embolization, in which it is produced by endogenously released substances.

   (Ref. Ganong 22th edition, Page 678)

   b. ***Coughing & sneezing*** : Coughing begins with a deep inspiration followed by forced expiration against a closed glottis. This increases the intrapleural pressure to 100 mm Hg or more. The glottis is then suddenly opened, producing an explosive outflow of air at velocities up to 965 km (600 miles) per hour. *Sneezing* is a similar expiratory effort with a continuously open glottis. These reflexes help expel irritants and keep airways clear.

   (Ref. Ganong 22th edition, Page 678)

   c. ***Responses in patients with heart-lung transplants*** : Trans plantation of the heart and lungs has progressed beyond experimental stage and is now established treatment for severe pulmonary disease and some other conditions. In individuals with transplants, the recipient's right atrium is sutured to the donor heart. and the donor heart does not reinnervate, so the resting heart rate is elevated. The donor trachea is sutured to the recipient's just above to carina, and afferent fibers from the lungs do not regrow. Consequently, healthy patients with heart-lung transplants provide an opportunity to evaluate the role of lung innervation in normal physiology. Their cough responses to stimulation of the trachea are normal, because the trachea remains innervated, but their cough responses to stimulation of the smaller airways are absent. Their bronchi tend to be dilated to a greater degree than normal. In addition, they have the normal number of yawns and sighs, indicating that these do not depend on innervation of the lungs. Finally, they lack Hering-Breuer reflexes, but their pattern of breathing at rest is normal, indicating that these reflexes do not play an important role in the regulation of resting respiration in humans.

   (Ref. Ganong 22th edition, Page 678)

   d. ***Afferents From "Higher Centers"*** : Pain and emotional stimuli affect respiration, so there must also be afferents from the limbic system and hypothalamus to the respiratory neurons in the brain stein. In addition, even though breathing is not usually a conscious event, both inspiration and expiration are under voluntary control.

The pathways for voluntary control pass from the neocortex to the motor neurons innervating the respiratory muscles, bypassing the medullary neurons.

Since voluntary and automatic control of respiration are separate, automatic control is sometimes disrupted without loss of voluntary control. The clinical condition that results has been called *Ondine's curse*. In German legend, Ondine was a water nymph who had an unfaithful mortal lover. The king of the water nymphs punished the lover by casting a curse upon him that took away all his automatic functions. In this state, he could stay alive only by staying awake and remembering to breathe. He eventually fell asleep from sheer exhaustion, and his respiration stopped. Patients with this intriguing condition generally have bulbar poliomyelitis or disease processes that compress the medulla.

(Ref. Ganong 22th edition, Page 679)

e. ***Afferents from proprioceptors*** : Carefully controlled experiments have shown that active and passive movements of joints stimulate respiration, presumably because impulses in afferent pathways from proprioceptors in muscles, tendons, and joints stimulate the inspiratory neurons. This effect probably helps increase ventilation during exercise.

(Ref. Ganong 22th edition, Page 679)

f. ***Respiratory components of visceral reflexes*** : The respiratory adjustments during *vomiting, swallowing, and sneezing* are inhibition of respiration and closure of the glottis. During these activities not only prevent the aspiration of food or vomitus into the trachea but, in the case of vomiting, fix the chest so that contraction of the abdoininal muscles increases the intra-abdominal pressure. Similar glottic closure and inhibition of respiration occur during voluntary and involuntary straining.

Hiccup is a spasmodic contraction of the diaphragm and other inspiratory muscles that produces an inspiration during which the glottis suddenly closes. The glottic closure is responsible for the characteristic sensation and sound. Hiccups occur in the *fetus in utero* as well as throughout extrauterine life. Their function is unknown. Most attacks of hiccups are of short duration, and they often respond to breath-holding or other measures that increase arterial Pco_2. Prolonged hiccuping can be debilitating. ***Yawning*** is a peculiar "infectious" respiratory act whose physiologic basis and significance are uncertain. Like hiccuping, it occurs in utero, and it occurs in fish and tortoises as well as mammals. Underventilated alveoli have a tendency to collapse, and it has been suggested that the deep inspiration and stretching open them and prevent the development of atelectasis. Yawning also increases venous return to the heart. Sighing may have a similar function. However, in actual experiments, no atelectatic effect of yawning could be demonstrated. It has also been suggested that yawning is a nonverbal signal used for communication between animals in a group, and one could argue that on a different level, the same thing is true in humans.

(Ref. Ganong 22th edition, Page 680)

g. ***Respiratory effects of baroreceptor stimulation*** : Afferent fibers from the baroreceptors in the carotid sinuses, aortic arch, atria, and ventricles relay to the respiratory neurons as well as the vasomotor and cardioinhibitory neurons in the medulla. Impulses in them inhibit respiration, but the inhibitory effect is slight and of little physiologic impor tance. The hyperventilation in shock is due to chemoreceptor stimulation caused by acidosis and hypoxia secondary to local stagnation of blood flow and is not baroreceptor-mediated. The activity of inspiratory neurons affects blood pressure and heart rate, and activity in the vasomotor and cardiac areas in the medulla may have minor effects on respiration.

(Ref. Ganong 22th edition, Page 680)

h. ***Effects of sleep*** : Respiration is less rigorously controlled during sleep than in the waking state, and brief periods of apnea occur in normal sleeping adults. There are variable changes in the ventilatory response to hypoxia. If the Pco_2 falls during the waking state, various stimuli from proprioceptors and the environment maintain respiration, but during sleep, these stimuli are decreased and a decrease in Pco_2 can cause apnea. During REM sleep, breathing is irregular and the CO_2 response is highly variable.

(Ref. Ganong 22th edition, Page 680)

4. **Hormonal eftects on respiration :** Ventilation is increased during the luteal phase of the menstrual cycle and during pregnancy. Experiments with animals indicate that this is due to activation of estrogen-dependent progesterone receptors in the hypothalamus. However, the physiologic significance of this increased ventilation is unknown.

(Ref. Ganong 22th edition, Page 678)

Role of medullary oscillatory circuit

The inspiratory and expiratory neurons complete a circuit between them known as "medullary oscillatory circuit" which play important role for the basic rhythm of respiration.

In the figure there are four inspiratory neurons on left side and four expiratory neuron on right side. Let us first consider inspiratory neuron. If one of the inspiratory neuron excited, it excites the next one, which excites the third one and so forth. This excitation continue around and around the inspiratory

circuit and as it doing so, colateral impulses are transm itted to inspiratory muscles for about 2 sec. In addition it also transmit inhi- bitory impulse to the expiratory net work. But just as soon as inspiratory oscillation ceases, there is no longer inhibition to expiratory net work. So the netural excitability of expiratory net work causes the expiratory oscillation. It continued for about 3 second.

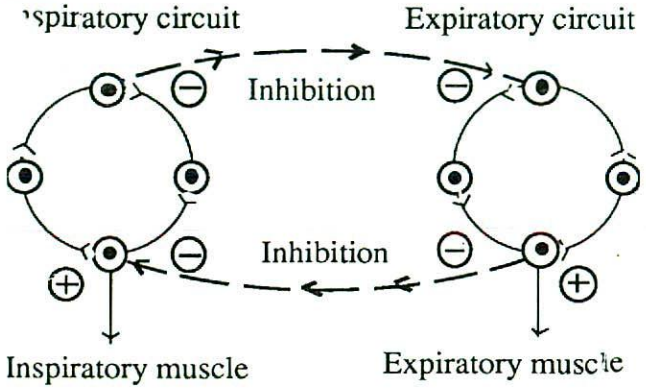


Fig. 7-13. *Medullary Oscillatory circuit.*

During this oscillation excitatory impulses are transmitted to expiratory muscles and inhibitory to the inspiratory network to keep it from oscillation. When the expiratory network stoped it oscillation, the inspiratory network begins to oscillate once again. In this way, medullary oscillatory circuit maintain normal rhythm of respiration.

Hering-Breuer Reflex

The rate and depth of respiration is controlled by the reflex which is transmitted from the stretch receptor of the lungs to the respiratory centre through the vagus nerve is called Hering Breuer reflex.

It has two parts :

1. *Hering Breuer inflation reflex :* When the air is inspired in the lungs, the stretch receptors in the wall of the lung stimulated and sends inhibitory impulse through the vagus nerve into the "tractus solitarius" of brain and then to the respiratory centre and thereby prevent further inflation. This is called Hering-Breuer inflation reflex.
2. *Hering Breuer deflation reflex :* The stretch receptors in the wall of the lung alveoli become unstretched during expiration. The impulses from these receptors ceases, which allows inspiration again and again. This is called Hering-Breuer deflation reflex.

Functions :

i. It is essential for the modification of continuous inspiration into rhythmic inspiration.
ii. It prevents the over distension of the lungs and thus protect it from burst.

Q. **Explain how respiration increases during exercise Or, Regulation of respiration during exercise.**

Ans. The factors that increase the rate and depth of respiration during exercise are summarized below-

a. *Nervous factor or direct stimulation of respiratory centre from motor cortex :* During exercise the brain transmitting impulses to the contracting muscles, also transmit colateral impulses to the respiratory centre. This stimulation of respiratory centre increases the rate of respiration.
b. *Indirect stimulation from proprioceptors* : During exercise, the movement of the limbs and body excites the proprioceptors. This then transmit impulses to the respiratory center which inturn increases the respiration. Beside this, during exercise hypoxia develops in the muscles that elicits afferent nerve signal to the respiratory center to excite respiration.
c. *Chemical factors* : During exercise the Pco_2 increases and Po_2 decreases. This then stimulate chemosensitive area of brain and peripheral chemoreceptor system, which then increase rate of respiration.

(Ref. Guyton & Hall-11th Edition, page 520)

Effects of bilateral section of phrenic nerves

Either the diaphragm or the external intercostal muscles alone can maintain adequate ventilation at rest. Transection of the spinal cord above the third cervical segment is fatal without artificial respiration, but transection below the fifth cervical segment is not, because it leaves the phrenic nerves that innervate the diaphragm intact; the phrenic nerves arise from cervical segments 3-5. Conversely, in patient with bilateral phrenic nerve palsy but intact innervation of their intercostal muscles, respiration is some what labored but adequate to maintain life. The scalen and sternocleidomastoid muscles in the neck are inspiratory muscles that help to elevate the thoracic cage during deep labored respiration.

Q. **What are the effect of transsection of one or two parts in the respiratory centre ?**

Ans.

1. When the medulla is transsected immediately above the medullary rhythmicity area and also immediately below this area basic rhythmicity occurs in at least some of the inspiratory neurons.
2. If the medulla is transsected immediately above the rhythmicity area but this area still connected to the spinal cord respiration occurs in gaps rather than in normal.
3. When the apneustic area is still connected to the medullary rhythmicity area but the pons has been transsected between the apneustic and pneumotaxic area - the pattern of prolonged inspiration and very short expiration occurs which is called apneusis.
4. When the afferent nerve fibres of vagus and of the glossopharyngeal nerves has been transsected - the apneustic pattern becomes specially marked.

5. When the vagus and pneumotaxic centre is transsected - very prolonged inspiration occurs.

Effects of exercise on respiration

Many cardiovascular and respiratory mechanisms must operate in an integrated fashion if the O_2 needs of the active tissue are to be met and the extra CO_2 and heat removed from the body during exercise. Circulatory changes increase muscle blood flow while maintaining adequate circulation in the rest of the body. There is in addition an increase in the extraction of O_2 from the blood in exercising muscles and an increase in ventilation that provides extra O_2, eliminates some of the heat, and excretes extra CO_2.

Changes in ventilation : Durine exercise, the amount of O_2 entering the blood in the lungs is increased because the amount of O_2, added to each unit of blood and the pulmonary blood flow per minute are increased. The Po_2 of blood flowing into the pulmonary capillaries falls from 40 to 25 mm of Hg or less, so that the alveolar capillary Po_2 gradient is increased and more O_2 enters the blood. Blood flow per minute is increased from 5.5 L/min to as much as 20-35 L/min. The total amount of O_2 entering the blood therefore increases from 250 mL/min at rest to values as high as 4000 mL/min. The amount of CO_2 removed from each unit of blood is increased, and CO_2 excretion increases from 200 mL/min to as much as 8000 mL/min. The increase in O_2, uptake is proportionate to work load up to maximum. Above this maximum O_2 consumption levels off and the blood lactate level continues to rise. The lactate comes from muscles in which aerobic resynthesis of energy stores cannot keep pace with their utilization and an *oxygen* debt is being incurred.

There is an abrupt increase in ventilation with the onset of exercise, followed after a brief pause by a further, more gradual increase. With *moderate exercise,* the increase is due mostly to an increase in the depth of respiration; this is accompanied by an increase in the respiratory rate when the exercise is more *strenuous*. There is an abrupt decrease in ventilation when exercise ceases, followed after a brief pause by a more gradual decline to pre-exercise values. The abrupt increase at the start of exercise is presumably due to psychic stimuli and afferent impulses from proprioceptors in muscles, tendons, and joints. The more gradual increase is presumably humoral even though arterial pH, Pco_2, and Po_2 remain constant during moderate exercise. The increase in ventilation is proportionate to the increase in O_2 consumption, but the mechanisms responsible for the stimulation of respiration are still the subject of much debate. The increase in body temperature may play a role. Exercise increases the plasma K^+ level, and this increase may stimulate the peripheral chemoreceptors. In addition, it may be that the sensitivity of the respiratory center to CO_2 is increased or that the respiratory fluctuations in arterial Pco_2 increase so that, even though the mean arterial Pco_2 does not rise, it is CO_2 that is responsible for the increase in ventilation. O_2 also seems to play some role despite the lack of a decrease in arterial Po_2, since during the perfonnance of a given amount of work, the increase in ventilation while breathing 100% O_2 is 10-20% less than the increase while breathing air. Thus, it currently appears that a number of different factors combine to produce the increase in ventilation seen during moderate exercise.

When ***exercise becomes more vigorous***, buffering of the increased amounts of lactic acid that are produced liberates more CO_2, and this further increases ventilation. With increased production of acid, the increases in ventilation and CO_2 production remain proportionate, so alveolar and arterial CO_2 change relatively little (*isocapnic buffering*). Because of the hyperventilation, alveolar Po_2 increases. With further accumulation of lactic acid, the increase in ventilation outstrips CO_2 production and alveolar Pco_2 falls, as does arterial Pco_2. The decline in arterial Pco_2 provides respiratory compensation for the metabolic acidosis produced by the additional lactic acid. The additional increase in ventilation produced by the acidosis is dependent on the carotid bodies and does not occur if they are removed.

The respiratory rate after exercise does not reach basal levels until the ***O_2 debt*** is repaid. This may take as long as 90 minutes. The stimulus to ventilation after exercise is not the arterial Pco_2 which is normal or low, or the arterial Pco_2, which is normal or high, but the elevated arterial H^+ concentration due to the lactic acidemia. The magnitude of the O_2 debt is the amount by which O_2 consumption exceeds basal consumption from the end of exertion until the O_2 consumption has returned to preexercise basal levels. During repayment of the O_2 debt, there is a small rise in the O_2 concentration in muscle myoglobin. ATP and phosphorylcreatine are resynthesizcd, and lactic acid is removed. Eighty percent of the lactic acid is converted to glycogen and 20% is metabolized to CO_2 and H_2O.

Because of the extra CO_2 produced by the buffering of lactic acid during strenuous exercis rises, R rises, reaching 1.5-2.0. After exertion, while debt is being repaid, the R falls to 0.5 or less.

(Ref. Ganong 22th edition, Page-681, 682)

Q. **What are the changes that occurs in respiratory system during exercise?**

Ans. The changes in the body that occurs during excercise is proportional to the intensity of exercise.

A. ***In moderate Excercise :***

1. *Pulmonary ventilation :* Pulmunary ventilation increases. *It is due to* -
   i. The alveolar PCO_2 of the subject rises and a large amount of CO_2 is diffuses to the alveolar air at each instant.
   ii. A rise of body temperature stimulates respiration

itself and also sensitizes the response of respiratory mechanism to the arterial PCO_2.

iii. A slight fall in arterial PO_2 which itself stimulate breathing, also sensitizes the respiratory response to PCO_2.

iv. Breathing is also stimulated by -

a. Reflexes from the moving joints.

b. Impulses from the higher centers.

2. *Oxygen usage :* This is increased. *It is due to* -

i. Breathing : The increase in pulmonary ventilation introduces large amounts of fresh air into the lung.

ii. O_2 Uptake in the lung : Large amount of oxygen are taken up from the lungs by the blood.

iii. Supply of oxygen to the tissues : A great blood supply to the muscle due to increased cardiac out put and redistribution of blood to the systemic circulation.

iv. Removal of oxygen by the tissues : This is effected as follows -

a. Dilatation and increase in the number of patent capillaries in the muscles slows the rate of the blood flow.

b. Low oxygen tension allows oxygen to diffuse more rapidly and to a greater extent.

c. High CO_2 tension and raised tamperature increases the extent and rate of dissociation of oxyhaemoglobin.

3. *Co_2 output :* Large amount of CO_2 is formed in the body, which is eleminated. *It is due to* -

i. Increased formation of CO_2.

ii. This increased CO_2 increase the PCO_2.

iii. Increased PCO_2 increases pulmonary ventilation causes rapid and more elemination of CO_2.

B. ***In severe Exercise :***

1. *Pulmonary ventilation* : Breathing remains much above the resting level for a prolonged period after the exertion is over.

2. *Lactic acid formation* : Lactic acid accumulates in the anoxic muscles and diffuses out into the blood stream and through out the body fluid.

3. *Respiratory quotient* : During the period of exertion first rises above 1 and may reach 1.5 or 2; attained maximum shortly after the end of exercise.

(Ref. Wright's. 13th Edition; page 214-17)

Oxygen debt

During exercise, the amount of O_2 entering the blood in the lungs is increasecd because the amount of O_2 added to each unit of blood and the pulmonary blood flow per minute are increased. The PO_2 of blood flowing into the pulmonary capillaries falls from 40 to 25 mm Hg or less, so that the alveolar-capillary PO_2 gradient is increased and more enters the blood. Blood flow per minute is increased from 5.5 liter/minute to as much as 20-35 liter/minute. The total amount of O_2 entering the blood therefore increases from 250 ml/minute at rest to values as high as 4000 ml/minute. The amount of CO_2 removed from each unit of blood is increased, and CO_2 excretion increases from 200 ml/minute to as much as 8000 ml/minute. The increase in O_2 uptake is proportionate to work load up to a maximum. Above this maximum, O_2 consumption levels off and the blood lactate level continues to rise. The lactate comes from muscles in which aerobic resynthesis of energy stores cannot keep pace with their utilization and an ***oxygen debt*** is being incurred.

(Ganong 22th Edition; page 681)

Respiratory insufficiency

Definition : Respiratory insufficiency means abnormalities in normal function of respiratory system. ***or***

Respiratory insufficiency means any type of abnormalities in normal rate and depth of respiration.

Causes of respiratory insufficiency :

i. Inadequate ventilation.

ii. Reduce gaseous diffusion through respiratory membrane.

iii. Abnormal ventilation- perfusion ratio.

(Ref. Guyton 10th edition)

Physiological basis of respiratory insufficiency

i. Some respiratory diseases result from inadequate ventilation.

ii. Whereas others result from abnormalities of diffusion through the pulmonary membrane or abnormal transport in the blood from the lungs to the tissues.

Diagnosis and treatment : The diagnosis and treatment of most respiratory disorders depend heavily on understanding the basic physiologic principles of respiration and gas exchange.

The therapy is often entirely different for these diseases, so it is no longer satisfactory simply to make a diagnosis of *respiratory insufficiency.*

(Ref. Guyton 10th Edition; page- 484)

Lung function tests

1. *Tests to evaluate the mechanics of the breathing by spirometer :*

a. Vital capacity (Male : 3.2 to 4.6 liter, Female : 2.9 to 4.2 liter)

b. Timed vital capacity or forced expiratory volume-FEV (80% in first hour)

c. Ventilatory boundaries of the lungs : The residual vlume (It is about 1200 ml) could not be determined

by spirometry. But it is estimated by means of nitrogen dilution technique.

2. Peak expiratory flow rate (about 6 to 15 liters/second)
3. *Test to evaluate the alvelolar ventilation :*
   a. Determination of dead spacce volume (In a young adult man *anatomical dead space* is about 150 ml).
   b. Uniform distribution of air measured by nitrometer.
4. *Test evaluating alveloar ventilation & perfusion ratio* (about 0.84) depending on continuous analysis of the carbon dioxide percentage of the expired air by carbondioxide analyser.
5. *Test involving the diffusing capacity :* By method of carbon monooxide diffusion measurement. The test envolving the Po_2 and Pco_2 and the blood by blood gas tensimeter of blood gases analyzer.
6. Measurement of maximum O_2 uptake (about 250 ml/minute).
7. Test to the efficiency of gaseous exchange at alveolar level (about 25 ml/mmHg/min).
8. Measurement of lung compliance (about 200 ml/cm of H_2O pressure).
9. *Test evaluating the pulmonary capillary blood (*about 7 mm Hg) *pressure :* These tests are uaually undertaken prior to removal of the lung or a portion of the lung. Before undertaken this procedure, cardiac catheterization is done and the tip of the catheter is passed through the pulmonary atery into the lung or the portion of the lung to be resected. If the pulmonary pressure is recorded to be normal and there is least chance of pulmonary oedema, the lung resection can be undertaken.
10. *Tests evaluating the functional integrity* of individual lobe of the lung by broncho-spirometer.
11. Bronchography.

(Ref. Ghosh and Sahana 2nd -381 & Concise Medical Physiology 2nd edition, page-190,191)

Tests done in the diagnosis of lungs diseases :

1. *X-ray chest P/A* (posterio-anterior) view & lateral view : For-Pneumonia, Pulmonary fibrosis, Tuberculosis, Sarcoidosis, Carcinoma etc.
2. *Sputum* microscopy and culture.
3. Spirometry
4. Arterial blood gas analysis
5. Bronchoscopy
6. CT Scanning etc.

Define the following

1. *Eupnea* : It means normal breathing.
2. *Tachypnea* : It means rapid breathing than normal.
3. *Bradypnea* : It means slow breathing than normal.
4. *Hypoxia* : It means decreased O_2 in tissue.
5. *Anoxia* : It means total lack of O_2.
6. *Hypoxemia* : It means reduced O_2 in blood.
7. *Hypercapnia* : It means excess CO_2 in blood.
8. *Hypocapnia* : It means depressed CO_2 in blood.
9. *Dyspnoea* : It means difficulty in breathing.
10. *Apnoea* : It means temporary cessation of breathing.
    1. *Voluntary apnoea* : Voluntary breath hold.
    2. *Involuntary apnoea* : During swallowing.

(Ref. Guyton & Hall-11th edition)

Hypoxia

Definition : Hypoxia is O_2 deficiency at the tissue level.

(Ref. Ganong 22th edition, Page 683)

Classification :

Hypoxia is classified in four types :

1. ***Hypoxic hypoxia*** *(anoxic anoxia)* : In this type of hypoxia PO_2 of the arterial blood is reduced.
   Here, O_2 carriage is normal but source of O_2 is less. It is the most common form of hypoxia seen clinically.

   Disoders causing hypoxic hypoxia :
   i. Lung failure (gas exchange failure)
      Pulmonary fibrosis
      Ventilation-perfusion imbalance
   ii. Shunt
   iii. Pump failure (ventilatory failure)
      Fatigue
      Mechenical defects
      Depression of respiratory controller in the brain.
2. ***Anaemic hypoxia*** : In this type of hypoxia the arterial PO_2 is normal but the amount of hemoglobin available to carry O_2 is reduced.
   It occurs due to-
   a. Lack of haemoglobin
   b. CO poisoning
   c. Abnormal Hb due to poisoning with nitrates, nitric oxide and other metals.
3. ***Stagnant or ischaemic hypoxia*** : In this type of hypoxia the blood flow to a tissue is so low that adequate O_2 is not delivered to it despite a normal Po_2 and hemoglobin concentration.
   It occurs due to-
   a. Decreased cardiac output due to heart failure.
   b. Decreased blood flow to the organ.
   c. Impaired venous return, haemorrhage and shock.
4. ***Histotoxic hypoxia*** : In this type of hypoxia, the amount of

O_2 delivered to a tissue is adequate but, because of the action of a toxic agent, the tissue cells can not make use of the O_2 supplied to them.

It occurs due to-

a. Poisoning with potassium cyanide which interferes tissue oxidation by paralysis the enzyme cytocrom oxidase.

b. Narcotics also depressed tissue oxidation by interfere with dehydrogenous system.

(Ref. Ganong 22th edition, Page-683, 684)

Causes of hypoxia

The following is a descriptive classification of the causes of hypoxia :

1. *Inadequate oxygenation of the lungs because of extrinsic reasons :*
   a. Deficiency of oxygen in atmosphere.
   b. Hypoventilation (neuromuscular disorders)
2. *Pulmonary disease :*
   a. Hypoventilation due to increased airway resistance or decreased pulmonary compliance.
   b. Uneven alveolar ventilation-perfusion ratio (including physiologic dead space and phy-siologic shunt)
   c. Diminished respiratory membrane diffusion.
3. *Venous to arterial shunts (right to left cardiac shunt).*
4. *Inadequate transport and delivery of oxygen :*
   a. Anaemia, abnormal hemoglobin.
   b. General circulatory deficicency
   c. Localized circulatory deficiency (Perip-heral, cerebral, coronary vessels)
   d. Tissue edema.
5. *Inadequate tissue capability of using oxygen :*
   a. Poisnoning of cellular enzymes.
   b. Diminished cellular metabolic capacity because of toxicity, vitamin dificiency or other factors.

(Ref. Guyton & Hall-11th Edition, page 530)

Effects of hypoxia

1. *Stagnant hypoxia* : The effects of stagnant hypoxia depend upon the tissue affected. Hypoxia due to slow circulation is a problem in organs such as the kidneys and heart during shock. The liver and possibly the brain are damaged by stagnant hypoxia in congestive heart failure. The blood flow to the lung is normally very large, and it takes prolonged hypotension to produce significant damage. However, ARDS can develop when there is prolonged circulatory collapse.
2. In *hypoxic hypoxia and the other generalized forms of hypoxia*, the brain is affected first. A sudden drop in the inspired Po_2 to less than 20 mm Hg, which occurs, for example, when cabin pressure is suddenly lost in a plane flying above 16,000m, causes loss of consciousness in 10-20 seconds and death in 4-5 minutes.
3. *Anemic hypoxia* : Hypoxia due to anaemia is not severe at rest unless the hemoglobin deficiency is marked, because red blood cell 2,3-DPG increases. However, anemic patients may have considerable difficulty during exercise because of limited ability to increase O_2 delivery to the active tissues.
4. *Less severe hypoxia* causes a variety of mental aberrations not unlike those produced by alcohol: impaired judgement, drowsiness, dulled pain sensibility, excitement, disorientation, loss of time sense, and headache. Other symptoms include anorexia, nausea, vomiting, tachycardia, and, when the *hypoxia is severe*, hypertension.
5. The rate of ventilation is increased in proportion to the severity of the hypoxia of the carotid chemoreceptor cells.

(Ref. Ganong 22th edition, Page 683, 690)

Treatment of hypoxia *:*

1. *Histotoxic Hypoxia* : Hypoxia due to inhibition of tissue oxidative processes is most commonly the result of cyanide poisoning. Cyanide inhibits cytochrome oxidase and possibly other enzymes. Methylene blue or nitrites are used to treat cyanide poisoning. They act by forming methemoglobin, which then reacts with cyanide to form cyanmethemoglobin, a nontoxic compound. The extent of treatment with these compounds is, of course, limited by the amount of methemoglobin that can be safely formed. Hyperbaric oxygenation may also be useful.
2. *Stagnant, anemic, and histotoxic hypoxia* : Adminis tration of oxygen-rich gas mixtures is of very limited value in stagnant, anemic, and histotoxic hypoxia because all that can be accomplished in this way is an increase in the amount of dissolved O_2 in the arterial blood.
3. *Hypoxic hypoxia* : Administration of oxygen-rich gas mixtures is of very limited value in hypoxic hypoxia when it is due to shunting of unoxygenated venous blood past the lungs. In other forms of hypoxic hypoxia, O_2 is of great benefit. Treatment regimes that deliver less than 100% O_2 are of value both acutely and chronically, and administration of O_2 24 hours per day for 2 years in this fashion has been shown to significantly decrease the mortality of chronic obstructive pulmonary disease.

(Ref. Ganong 22th edition, Page-691)

Hypercapnia

Retention of CO_2 in the body (hypercapnia) initially stimulates respiration. Retention of larger amounts produces symptoms due to depression of the central nervous system: confusion, diminished sensory acuity, and, eventually, coma with respiratory depression and death. In patients with these symptoms, the Pco_2 is markedly elevated, there is severe

respiratory acidosis, and the plasma HCO_3^- may exceed 40 meq/L. Large amounts of HCO_3^- are excreted, but more HCO_3^- is reabsorbed, raising the plasma HCO_3^- and partially compensating for the acidosis.

CO_2 is so much more soluble than O_2 that hypercapnia is rarely a problem in patients with pulmonary fibrosis. However, it does occur in ventilation-perfusion inequality and when for any reason alveolar ventilation is inadequate in the various forms of pump failure. It is exacerbated when CO_2 production is increased. For example, in febrile patients there is a 13% increase in CO_2 production for each 1°C rise in temperature, and a high carbohydrate intake increases CO_2 production because of the increase in RQ. Normally, alveolar ventilation increases and the extra CO_2 is expired, but it accumulates when ventilation is compromised.

(Ref. Ganong 22th edition, Page 692)

Hypocapnia

Hypocapnia is the result of hyperventilation. During voluntary hyperventilation, the arterial Pco_2 falls from 40 to as low as 15 mm Hg while the alveolar Po_2 rises to 120-140 mm Hg.

The more chronic effects of hypocapnia are seen in neurotic patients who chronically hyperventilate. Cerebral blood flow may be reduced 30% or more because of the direct constrictor effect of hypocapnia on the cerebral vessels. The cerebral ischemia causes light-headedness, dizziness, and paresthesias. Hypocapnia also increases cardiac output. It has a direct constrictor effect on many peripheral vessels, but it depresses the vasomotor center, so that the blood pressure is usually unchanged or only slightly elevated.

Other consequences of hypocapnia are due to the associated respiratory alkalosis, the blood pH being increased to 7.5 or 7.6. The plasma HCO_3^- level is low, but HCO_3^- reabsorption is decreased because of the inhibition of renal acid secretion by the low Pco_2. The plasma total calcium level does not change, but the plasma Ca^{2+} level falls and hypocapnic individuals develop carpopedal spasm, a positive Chvostek sign, and other signs of tetany.

(Ref. Ganong 22th edition, Page 692)

Cyanosis

Reduced hemoglobin has a dark color, and a dusky bluish discoloration of the tissues, called cyanosis, appears when the reduced hemoglobin concentration of the blood in the capillaries is more than 5 gm/dl. Minimum 5 gm/dl of deoxygenated Hb is necessary for cyanosis.

(Ref. Ganong 22th edition, Page 684)

Sites of cyanosis examination :

i. Nail beds
ii. Mucous membranes
iii. Earlobes
iv. Lips
v. Fingers, where the skin is thin.
vi. Tip of the nose
vii. Tip of the tongue etc.

(Ref. Ganong 22th edition, Page 683)

Its occurance depends upon :

1. Total amount of hemoglobin in blood.
2. Degree of Hb unsaturation.
3. State of capillary circulation.
4. Pigmentation and thickness of the skin.

(Ref. Ganong 22th edition, Page 684)

Types of cyanosis :

a. Central cyanosis : It occurs in the tip of the tongue.
b. Peripheral cyanosis : It occurs in the lips, nose, ear lobules, nail bed etc.

Cyanosis does not occur in-

1. Anemic hypoxia : Because the total hemoglobin content is low.
2. Carbon monoxide poisoning : Because the color of reduced hemoglobin is obscured by the cherry red color of carbon-monoxyhemoglobin.
3. Histotoxic hypoxia : Because the blood gas content is normal.

A discoloration of skin and mucouse membrane similar to cyanosis is produced by high circulating levels of methemoglobin.

(Ref. Ganong 22th edition, Page 684)

Emphysema

The term pulmonary emphysema means excess air in the lungs. But chronic pulmonary emphysema is a complex destructive process of lungs. It is caused by tobacco smoking.

Effect of Empysema :

i. The bronchial obstruction increases airway registance that causes hypoventilation.
ii. Loss of alveolar wall decreases lung diffusing capacity.
iii. Abnormal ventilation-perfusion ratio.
iv. Pulmonary hypertension. Because loss of lung parenchyma also decreases pulmonary capillary.
v. Due to these, the person develop hypoxia and hypercapnia causing death.

Pneumonia

Definition : The term pneumonia describes any inflammatory condition of lung in which the alveoli are usually filled with fluid and blood cells.

Cause : It is caused by bacteria Pneumococci.

Effect :

1. Reduction of the total surface area of respiratory membrane.

2. Decreased ventilation perfusion ratio.
3. Reduced diffusing capacity.

Pulmonary Hypertension

Sustained elevations of pulmonary arterial pressure can occur in infants and adults. In many cases in adults the cause is unknown, but pulmonary arterial pressure elevation can occur in people who inhale cocaine and in people who take dexfenfluramine and related appetite suppresent drugs that increase serotonin. Pressure elevation eventually leads to right heart failure and death.

Treatment : Vasodilators including prostacycline (epopros tenol) is of value.

(Ref. Ganong 22th Edition)

Atelectasis

Atelectasis means collapse of the alveoli, either in a localized area or in an entire lobe, or in an entire lung.

Cause :

1. Obstruction of airways
2. Lack of surfactant in the fluid lining the alveoli.

Asthma

Asthma is characterized by spastic contraction of the bronchioles which causes extremely difficult breathing.

Cause : Hypersensivity of the bronchioles to foreign substances in the air, plant pollens, smog etc.

Effect :

1. Increased air way resistance.
2. Difficulty in expiration but inspiration is normal.
3. Reduced maximum expiratory rate and timed expiratory volume.
4. Increased functional residual capacity and residual volume.

Tuberculosis (lung)

Ans. In tuberculosis, the tubercle bacilli cause a *peculiar tissue reaction in the lungs*, including-

i. Invasion of the infected tissue by macrophages

ii. *Walling off* of the lesion by fibrous tissue to form the so called tubercle. This walling-off process helps to limit further transmission of the tubercle bacilli in the lungs and therefore is part of the protective process against extension of the infection.

iii. However, in about 3 per cent of all people who develop tuberculosis, if untreated, the walling-off process fails and tubercle bacilli spread throughout the lungs, often causing extreme destruction of lung tissue with formation of large abscess cavities.

iv. Thus, tuberculosis in its late stages is characterized by many areas of fibrosis throughout the lungs as well as reduced total amount of functional lung tissue.

These effects cause :

a. Increased *work* on the part of the respiratory muscles to cause pulmonary ventilation and *reduced vital capacity* and *breathing capacity.*

b. *Reduced total respiratory membrane surface area* and *increased thickness of the respiratory membrane*, causing progressively diminished pulmonary diffusing capacity.

c. Abnormal *ventilation-perfusion ratio* in the lungs, further *reducing overall pulmonary diffusion of oxygen* and *carbon dioxide.*

(Ref Guyton & Hall-11th Edition; page 530)

Acclimatisation

The term acclimatisation means the adjustment of the human body to suit the climate at a higer altitude (between 3050-4260 meters).

The five principal means by which acclimatisation comes about are :

1. Increased pulmonary ventilation.
2. Increased haemoglobin in the blood.
3. Increased diffusion capacity of the lungs.
4. Increased vascularity of the tissues and.
5. Increased ability of the cells to utilize oxy-gen despite the low Po_2.

(Ref Guyton & Hall-11th Edition; page 519)

Artificial respiration

Definition : Artificial respiration is a life saving process when normal respiration will ceases with persistance normal heart beat. This must be applied within 8 minutes of ceasation of respiration.

Purposes of artificial respiration :

1. By maintaining the gaseous exchange, the vitality of nerve center is miantained. It is expected that after sometimes respiratory center will start functioning spontaneously.
2. During artificial respiration the alternate inflation and deflation of lungs reflexly stimulate the respiratory center and thus help them to take up their own rhythm.

Types of artificial respiration

There are two types of artificial respiration :

A. *Manual :*
   i. Mouth to mouth method
   ii. Arm lift back pressure method.

B. *Mechanical :*
   i. Tank respiratory method.
   ii. Brag paul method.

Indications of Artificial Respiration :

i. Drawning.

ii. Deep anesthesia during surgical operation.

iii. Carbon monooxide poisoning
iv. Electric shock.
v. Encephalities affecting respiration.

Asphyxia

In asphyxia produced by occlusion of the airway, acute hypercapnia and hypoxia develop together. There is pronounced stimulation of respiration, with violent respiratory efforts. Blood pressure and heart rate rise sharply, catecholamine secretion is increased, and blood pH drops. Eventually the respiratory efforts cease, the blood pressure falls, and the heart slows. Asphyxiated animals can still be revived at this point by artificial respiration, although they are prone to ventricular fibrillation, probably because of the combination of hypoxic myocardial damage and high circulating catecholamine levels. If artificial respiration is not started, cardiac arrest occurs in 4-5 minutes.

(Ref. Ganong 22th edition, Page-692)

Scuba *(self contained under water breathing apparatus)* **diving**

Introduction : Before the 1940s, almost all diving was done using a diving helmet connected to a hose through which air was pumped to the diver from the surface. Then, in 1943, Jacques Cousteau developed and popularized the *self-contained underwater breathing apparatus*, popularly known as the SCUBA apparatus.

The type of SCUBA apparatus used in more than 99 percent of all sports and commercial diving is the open-circuit demand system.

Components :

i. One or more tanks of compressed air or some other breathing mixture
ii. A first-stage *reducing* valve for reducing the very high pressure from the tanks to a low pressure level
iii. Combination inhalation *demand* valve and exhalation valve that allows air to be pulled into the lungs with slight negative pressure of breathing and then to be exhausted into the sea at a pressure level slightly positive to the surrounding water pressure.
iv. A mask and tube system with small *dead space.*

The demand system operates as follows : The first stage reducing valve reduces the pressure from the tanks so that the air delivered to the mask has a pressure slightly greater than the surrounding water pressure. The breathing mixture does not flow continually into the mask. Instead, with each inspiration, slight negative pressure in the demand valve of the mask pulls the diaphragm of the valve open, and this automatically releases air from the tank into the mask and lungs. In this way, only the amount of air needed for inhalation enters the mask. Then, on expiration, the air cannot go back into the tank but instead is expired into the sea.

The most important problem in use of the SCUBA is the limit on the amount of time one can remain beneath the surface ; for instance, only a few minutes are possible at a 200-foot depth. The reason for this is that tremendous airflow from the tanks is required to wash carbon dioxide out of the lungs - the greater the depth, the greater the airflow in terms of *quantity* of air per minute that is required because the *volumes* have been compressed to sizes.

(Ref Guyton & Hall-11th Edition; page-549)

Drowning

Drowning is suffocation by immersion, usually in water. In about 10% of drownings, the first gasp of water after the losing struggle not to breathe triggers *laryngospasm*, and *death* results from asphyxia without any water in the lungs.

In the remaining cases, the glottic muscles eventually relax and fluid enters the lungs. Fresh water is rapidly absorbed, diluting the plasma and causing *intravascular hemolysis*.

Ocean water is markedly hypertonic and draws fluid from the vascular system into the lungs, decreasing plasma volume.

The immediate *goal in the treatment* of drowning is, of course, resuscitation, but long-term treatment must also take into account the circulatory effects of the water in the lungs.

(Ref. Ganong 22th edition, Page-692)

Periodic Breathing

The acute effects of voluntary hyperventilation demonstrate the interaction of the chemical respiratory regulating mechanisms. When a normal individual hyperventilates for 2-3 minutes, then stops and permits respiration to continue without exerting any voluntary control over it, there is a period of *apnea*. This is followed by a few shallow breaths and then by another period of apnea, followed again by a few breaths (*periodic breathing*).

The cycles may last for some time before normal breathing is resumed. The apnea apparently is due to CO_2 lack because it does not occur following hyperventilation with gas mixtures containing 5% CO_2. During the apnea, the alveolar Po_2 falls and the Pco_2 rises. Breathing resumes because of hypoxic stimulation of the carotid and aortic chemoreceptors before the CO_2 level has returned to normal. A few breaths eliminate the hypoxic stimulus, and breathing stops until the alveolar Po_2, falls again. Gradually, however, the Pco_2, returns to normal, and normal breathing resumes.

(Ref. Ganong 22th edition, Page-692)

Cheyne-Stoke respiration

Periodic breathing occurs in various disease states and is often called *Cheyne-Stokes respiration.*

It is seen most commonly in patients with congestive heart failure and uremia, but it occurs also in patients with brain disease and during sleep in some normal individuals.

Some of the patients with *Cheyne-Stokes respiration* have increased sensitivity to CO_2. The increased response is

apparently due to disruption of neural pathways that normally inhibit respiration. In these individuals, CO_2 causes relative hyperventilation, lowering the arterial Pco_2. During the resulting apnea, the arterial Pco_2 again rises to normal, but the respiratory mechenism again overresponds to CO_2. Breathing ceases, and the cycle repeats.

Another cause of periodic breathing in patients with cardiac disease is prolongation of the lung-to-brain circulation time, so that it takes longer for changes in arterial gas tensions to affect the respiratory area in the medulla. When individuals with a slower circulation hyperventilate, they lower the Pco_2 of the blood in their lungs, but it takes longer than normal for the blood with a low Pco_2 to reach the brain. During this time, the Pco_2 in the pulmonary capillary blood continues to be lowered, and when this blood reaches the brain, the low Pco_2 inhibits the respiratory area, producing apnea. In other words, the respiratory control system oscillates because the negative feedback loop from lungs to brain is abnormally long.

(Ref. Ganong 22th edition, Page-693)

Biots breathing

It is characterized by several normal respiration at a time (1-5 or more) followed suddenly by a period of complete cessation of respiration and so on.

(Ref. Guyton 11th Edition)

Condition where found : Is seen in meningitis and other diseased condition like contusion, concussion of brain etc.

Sleep Apnea

Episodes of apnea during sleep can be central in origin, ie, due to failure of discharge in the nerves producing respiration, or they can be due to airway obstruction (*obstructive sleep apnea*).

This can occur at any age and is produced when the pharyngeal muscles relax during sleep. In some cases, failure of the genioglossus muscles to contract during inspiration contributes to the blockage: these muscles pull the tongue forward, and when they do not contract the tongue falls back and obstructs the airway. After several increasingly strong respiratory efforts, the patient wakes up, takes a few normal breaths, and falls back to sleep. Not surprisingly, the apneic episodes are most common during REM sleep, when the muscles are most hypotonic.

The *symptoms* are loud snoring, morning headaches, fatigue, and day time sleepiness.

When severe and prolonged, the condition is said to increase the incidence of pulmonary hypertension, heart failure, myocardial infarction, and stroke. In addition, the incidence of motor vehicle accidents in sleep apnea patients is seven times greater than it is in the general driving population.

(Ref. Ganong 22th edition, Page-693)

Sudden Infant Death Syndrome

It has been argued that sudden infant death syndrome (SIDS) may be a form of sleep apnea. This disorder, in which apparently healthy infants are found dead, often in their cribs, has attracted a great deal of attention. Apneic spells are common in premature infants. However, periods of prolonged apnea do not correlate with the subsequent occurrence of death, and none of the known tests of chemoresponsiveness reliably predict which infants will subsequently have difficulty. Some of the cases appear to be caused by cardiac arrhythmias complicating the congenital long QT syndrome. In addition, there is evidence that the incidence of SIDS is increased in infants of mothers who smoke. It is increased also by sleeping in the prone position and teaching mothers to put their babies down on their backs has led to a significant reduvtion in incidence.

(Ref. Ganong 22th edition, Page-693)

Q. 14. **Short notes on- decompression sickness.**

Ans. Decompression sickness :

I. *Definition* : Decompression sickness (*the bend', caisson disease*) occurs when the diver ascend to the surface too rapidly.

II. *Cause* : It is caused by the release of inert gases, usually nitrogen or helium, which form bubbles in the tissue (both extracellular and intracellular space) as the ambient pressure falls.

Normally at sea level 1 liter of nitrogen is dissolved in the entire body (less than half in the body water and reminder in the fat). Nitrogen is not metabolized in the body - hence it remains dissolved state.

III. *Clinical features* : Symptoms commonly appear 10-30 minutes after the diver resurfaces.

1. Non -neurological or type I bends (due to bubbles in the tissue) :
   a. Skin irritation
   b. Joint pain.
2. Neurological (type 2 bends)
   a. Cortical blindness
   b. Hemiparesis
   c. Sensory disturbances.

   These features are due to bubbles in the blood stream that obstruct the arteries to the brain and spinal cord. If nitrogen bubbles occur in the pulmonary vessels, divers experiences :
   * Retrosternal discomfort
   * Dyspnoea
   * Cough.
3. Long term problem: Aseptic necrosis caused by infraction due to nitrogen bubbles lodging in nutrient arteries supplying bone.

(N.B. Ascent in an airplane is equivalent to ascent from a dive).

Shock-lung syndrome

In severe shock deterioration of the lungs also often leads to

respiratory distress and death several days later- called the shock lung syndrome.

(Ref. Guyton & Hall-11th Edition)

Oxygen toxicity

It is interesting that while O_2 is necessary for life in aerobic organisms, it is also toxic. Indeed, 100% O_2 has been demonstrated to exert toxic effects not only in animals but also in bacteria, fungi, cultured animal cells, and plants.

Cause : The toxicity seems to be due to the production of the superoxide anion (O_2^-), which is a free radical and H_2O_2.

Effects :

i. When 80%-100% O_2 is administered to humans for periods of 8 hours or more, the respiratory passages become irritated, causing substernal distress, nasal congestion, sore throat, and coughing.

ii. Some infants treated with O_2 for respiratory distress syndrome develop a chronic condition characterized by *lung cysts* and *densities* (*bronchopulmonary dysplasia*). There is evidence that this syndrome is a manifestation of O_2 toxicity. Another complication in these infants is *retinopathy* of prematurity (*retrolental fibroplasia*), the formation of opaque vascular tissue in the eyes, which can lead to serious visual defects. The retinal receptors mature from the center to the periphery of the retina, and they use considerable O_2. This causes the retina to become vascularized in an orderly fashion. Oxygen treatment before maturation is complete provides the needed O_2 to the photoreceptors, and consequently the normal vascular pattern fails to develop.

Treament : There is evidence that this condition can be prevented or ameliorated by treatment with *vitamin E*, which exerts an antioxidant effect, and, in animals, by growth hormone inhibitors.

(Ref. Ganong 22th Edition; page 691)

(Q. 00. Write short notes on- acute oxygen posioning)

Hyperbaric oxygen therapy

Administration of 100% O_2 at increased pressure accelerates the onset of O_2 toxicity, with the production not only of tracheobronchial irritation but also of muscle twitching, ringing in the ears, dizziness, convulsions, and coma. The speed with which these symptoms develop is proportionate to the pressure at which the O_2 is administered; eg, at 4 atmospheres, symptoms develop in half the subjects in 30 minutes, whereas at 6 atmospheres, convulsions develop in a few minutes. Administration of other gases at increased pressure also causes central nervous system symptoms. Administration of O_2 at elevated pressures to rats decreases their brain GABA content and their brain, liver, and kidney ATP content.

On the other hand, exposure to 100% O_2 at 2-3 atmospheres can increase dissolved O_2 in arterial blood to the point that arterial O_2 tension is greater than 2000 mm Hg and tissue O_2 tension is 400 mm Hg. If exposure is limited to 5 hours or less at these pressures, O_2 toxicity is not a problem.

Therefore, ***hyperbaric O_2 therapy*** in closed tanks is used to treat diseases in which improved oxygenation of tissues can not be achieved in other ways.

Indication of hyperbaric O_2 therapy : It is of demonstrated value in-

i. Carbon monoxide poisoning
ii. Radiation-induced tissue injury
iii. Gas gangrene
iv. Very severe blood loss anemia
v. Diabetic leg ulcers and other wounds that are slow to heal
vi. Rescue of skin flaps and grafts in which the circulation is marginal.
vii. It is also the primary treatment for decompression sickness and air embolism.

(Ref. Ganong 22th Edition; page 691)

(Q. 00. Short notes on- Hyper baric oxygen therapy)

Introduction 7.40 | *Inspiration & Expiration 7.42* | *Transport of O2 & CO2 7.45* | *Applied 7.51-7.54*
Pulmonary Circulation 7.41 | *Pulmonary Ventilation 7.43* | *Regulation of Respiration 7.49*

***Direction** : Write 'T' for true & 'F' for false against each of the following statement.*

Introduction

Q. 01. **There are about .. million alveoli in man**
- T a. 300
- F b. 50
- F c. 100
- F d. 500
- F e. 200

Q. 02. **Breath rate at rest (adult)**
- T a. breathes 12-18 times/minute.
- T b. breathes 6-8 L/min.
- T c. inhales about 250 ml of O_2/minute
- F d. exhales about 150 ml of CO_2/minute.
- F e. ventilates 400 ml of air per breath.

Q. 03. **Functions of nose include**
- T a. warming the air.
- T b. humidifying the air.
- T c. partially filtering the air.
- T d. helping in olfaction.
- T e. conduction of air.

Q. 04. **Non-respiratory functions of the lungs are**
- T a. Synthesis of prostaglandins.
- T b. Activation of angiotensin-I to angiotensin-II.
- T c. Release of histamine.
- F d. Synthesis of 5-hydroxy tryptamine.
- F e. Transport of O_2 and CO_2.

Q. 05. **Non-respiratory function of the lung is**
- T a. Serotonin metabolism
- F b. Dopamine metabolism
- F c. Adrenaline metabolism
- F d. PGE2 production.
- F e. PGI production.

Q. 06. **Lung defence mechanisms include**
- T a. Mucus secretion
- T b. Macrophages
- T c. Lung fluids
- F d. Negative intraplural pressure
- F e. Surfactant.

Q. 07. **Compliance of the lungs**
- T a. in adult is about 200 ml/cm of water transpulmonary pressure.
- T b. is greater in adults than in infants.
- T c. is gteater when filled with nonnal saline than filled with air.
- T d. is greater when they axe expanded with normal tidal volume.
- F e. is greater in recumbent subjects than in standing.

Q. 08. **Compliance of the lung, is decreased in this conditions**
- T a. Fibrosis of lung
- T b. Pulmonary oedema
- T c. Kyphosis
- F d. Emphysema
- F e. All.

Q. 09. **Surfactant**
- T a. is secreted by type II alveolar epithelial cells.
- T b. increases the lung compliance.
- T c. increases in the fetal lungs during the last month of pregnancy.
- F d. increases the surface-tension of the fluid lining alveolar walls.
- F e. causes collapsing of the lungs.

Q. 10. **Surfactant**
- T a. decreases surface tension.
- T b. is formed by type-II alveolar epithelial cell
- T c. lack causes atelectasis.
- T d. is responsible to prevent collapsing tendency of lungs.
- F e. is secreted by type-I alveolar epithelial cell.

Q. 11. **Surfactant**
- T a. Is composed of phospholipids.
- T b. Is composed of dipalmitoyl lecithin.
- T c. Contains protein.
- T d. Decreases surface tension.
- F e. Is secreted by type-I alveolar epithelium.

Q. 12. **The surfactant material lining the lung alveoli**
- T a. Decreases the surface tension of alveolar fluid

T b. Increases the compliance of lungs
T c. Has increasingly less effect, the more lungs are inflated
T d. Is decreased when pulmonary blood flow is interrupted
F e. Is secreted by type-I alveolar epithelium.

Q. 13. **Instability of alveoli does not occur due to**
T a. Interdependence
T b. Fibrous tissue
T c. Surfactant
F d. Elastic tissue of lungs
F e. Due to negative intrapleural pressure.

Q. 14. **Work done in quiet breathing is**
T c. 0.5 Kg-m/min
F a. 0.1 Kg-m/min
F b. 0.2 Kg-m/min
F d. 2.5 Kg-m/min
F e. 1.5 Kg-m/min

Q. 15. **The work of breathing**
T a. increases when the subject exercises.
T b. increases when the subject lies down.
T c. comprises compliance work, tissue resistance work and airway resistance work.
F d. increases when lung compliance increases.
F e. decreases in asthma.

Q. 16. **Increased fetal cortisol just before birth results in**
T a. Fetal lung maturation
F b. Uterine contraction
F c. Release of oxytocin
F d. Placental steroid biogenesis
F e. All.

Q. 17. **Pulmonary wedge pressure is**
T a. Usually 2-3 mm of Hg.
T b. Mesaured in a perosn with right sided heart failure.
T c. Measured by floating a baloon-tipped catheter to right heart.
F d. Measured by a baloon-tipped catherer to left heart.
F e. All.

Q. 18. **Effort during normal respiration is done due to**
T a. Creating negative pleural pressure
F b. Lung elasticity
F c. Respiratory air passages
F d. Alveolar air spaces
F e. None.

Q. 19. **Respiratory quotient of cerebral tissue is**
T a. 0.95-0.99
F b. 0.75 -0.95
F c. 1.0-1.1
F d. 1.1-1.2
F e. 1.95-1.99

Q. 20. **Liver has the maximum O_2 consumption (51 ml/min), the next organ to have the maximum O_2 (ml/min) is :**
T a. Skeletal muscle
F b. Heart
F c. Brain
F d. Kidney
F e. Skin.

Q. 21. **Respiratory minute volume in a normal person**
T a. 6.0 L/min
F b. 1.2 L/min
F c. 2.1 L/min
F d. 4.2 L/min
F e. 4.0 L/min

Q. 22. **The oxygen consumption of human brain is**
T a. 3.5 ml/100 gm brain/min
F b. 1.0 ml/100 gm brain/min
F c. 1.5 ml/100 gm brain/min
F d. 5.0 ml/100 gm brain/min
F e. 0.5 ml/100 gm brain/min

Q. 23. **Oxygen consumption of whole human brain in ml/minute is about**
T a. 49
F b. 29
F c. 35
F d. 61
F e. 39

Q. 24. **Oxygen consumption of renal cortex and inner medulla are ml/100 gm/min respectively**
T a. 9, 4
F b. 9, 0, 4
F c. 4, 9
F d. 9, 4, 1
F e. 0, 4, 6

Pulmonary Circulation

Q. 25. **Pulmonary circulation**
T d. blood flow is about 9% of total blood volume.
T e. vascular resistance is less than that of systemic vascular resistance.
T a. arterial mean pressure is about 15 mml-Ig.
T b. capillary pressure is 7 mmHg.
F c. blood flow is about 4 litres/min.

Q. 26. **Regarding blood pressure in pulmonary circulation**
T a. Pulmonary artery systemic pressure is about 25 mm of Hg.

T b. Pulmonary artery diastolic pressure is about 8 mm of Hg.
T c. Pulmonary capillary pressure is about 7 mm of Hg
T d. Left atrial and pulmonaiy venous pressure are average 2mm of Hg.
F e. Mean pulmonary pressure is about 7 mm of Hg.

Q. 27. **As blood passes through systemic capillaries**
T a. its O_2 dissociation curve shifts to the right.
T b. its ability to deliver O_2 to the tissues is enhanced.
T c. HCO_3 ions pass from red cells to plasma.
F d. pH rises.
F e. Cl^- ion concentration in red cells falls.

Q. 28. **Factors preventing pulmonary edema are**
T a. Normal negativity of the interstitial fluid pressure.
T b. Lymphatic pumping of fluid out of the interstitial spaces.
T c. Decreased colloid osmotic pressure of interstitial fluid.
F d. Increased interstitial fluid pressure
F e. Increased intra alveolar pressure.

Q. 29. **Ventilation perfusion ratio is maximum in**
T a. Apex of lung
F b. Base of lung
F c. Post lobe of lung
F d. Middle lobe of lung
F e. All.

Q. 30. **Rise of pulmonary arterial pressure is caused by**
T a. Hypoxia
F b. Acidosis
F c. Alkalosis
F d. All of the above
F e. Cyanosis.

Q. 31. **When the atmospheric pressure is halved, which of the following is not likely to develop?**
T a. A rise in cerebral blood flow
F b. An increase in pulmonary ventilation
F c. A fall in arterial PO_2
F d. A rise in arterial pH
F e. None.

Q. 32. **In normal adult, the lung is kept dry because of**
T a. Hydrostatic pressure
F b. Osmotic pressure
F c. Surfactant
F d. Tidal volume
F d. None.

Q. 33. **Pulmonary wedge pressure corresponds to**
T a. Left atrial pressure
F b. Right atrial pressure
F c. Right ventricular pressure
F d. None.
F e. Left ventricular pressure

Inspiration & Expiration

Q. 34. **During inspiration**
T a. heart rate is increased.
T b. more energy is expended than during expiration.
T c. venous return is increased.
F d. lung expansion is assisted by surface tension forces in the alveoli.
F e. lung expansion begins when intrapleural pressure fafls below atmospheric pressure.

Q. 35. **During quite inspiration**
T a. The diaphragm contract
T b. The intrapleural pressure becomes more negative
T c. The intra-alveolar pressure is lower than the atmospheric pressure
F d. Intra-abdominal pressure decreases
F e. surfactant deficiency is associated with a more negative intra-alveolar pressure than normal.

Q. 36. **Expiration**
T a. Is driven by elastic recoil of the lungs during quite breathing.
T b. May be accelerated by actively increasing the intra abdominal pressure.
T c. Is associated with a positive intra-alveolar pressure during quite breathing.
F d. Associated with a a positive intrapleural pressure during breathing.
F e. Is an active process.

Q. 37.**Muscle of expiration**
T a. Rectus abdominis.
F b. Diaphragm
F c. Internal intercostal
F d. External intercostal
F e. None.

Q. 38. **Relaxation of bronchial smooth muscle is induced by**
T a. Vasoactive intestinal polypeptide.
F b. Leukotrienes.
F c. Acetylecholine.
F d. Aold air.
F e. Sulfur dioxide.

Q.39. **Bronchial smooth muscle contracts in response to**
T a. parasympathetic stimulation.
T b. inhalation of cold air.
T c. bronchial mucosal irritation.
F d. local beta adrenoceptor stimulation.
F e. circulating noradrenaline.

Q. 40. **During inspiration there is a fall in**
- T a. intrathoracic pressure.
- T b. intra-pleural pressure.
- T c. intrapulmonary pressure.
- F d. intra abdominal pressure.
- F e. dead space volume.

Q. 41. **The intrapleural pressure at the end of deep inspiration is**
- T a. - 4 mm Hg
- F b. + 4 mm Hg
- F c. - 18 mm Hg
- F d. + 18 mm Hg
- F e. - 7 mm Hg

Q. 42. **During the initial part of inspiration, which of the following does not occur?**
- T a. Intrathoracic pressure rises
- F b. Intrapulmonary pressure falls
- F c. Intrabdominal pressure rises
- F d. The partial pressure of O_2 in dead space rises.
- F e. All.

Pulmonary Ventilation

Q. 43. **In normal lungs**
- T a. the tidal volume is about 500 ml.
- F b. the expiratory reserve volume is 1200 ml.
- F c. the tidal volume is the volume of air inspired or expired per minute.
- F d. the functional residual capacity equals the tidal volume plus the expiratory reserve volume.
- F e. the total lung capacity is about 4600 ml.

Q. 44. **The approximate dead space of a normal 70-kg man breathing normal air is**
- T a. 150 ml
- F b. 230 ml
- F c. 180 ml
- F d. 280 ml
- F e. 380 ml.

Q. 45. **Total dead space can be calculated from**
- T a. PCO_2 of expired air
- T b. PCO_2 of alveolar gas
- T c. Tidal volume
- T d. All of the above
- T e. None of the above

Q. 46. **In an normal adult, the ratio of physiological and anatomical dead space is**
- T a. 1 : 1
- F b. 2 : 1
- F c. 1 : 3
- F d. 3 : 1
- T e. 4 : 1

Q. 47. **Respiratory dead space**
- T a. Is about 150 ml in young adult.
- T b. Increases slightly with age.
- T c. Sturates inspired air with water vapour.
- F d. Decreases during deep inspiration.
- F e. Takes part in gaseous exchange.

Q. 48. **Ventilation is increased**
- T a. when plasma CO_2 level is raised.
- T b. during chronic renal failure.
- T c. during muscular exercise.
- T d. at a high altitude.
- F e. during deep sleep.

Q. 49. **At high altitude, there is an increase in**
- T a. arterial pH.
- T b. diffusing capacity of the lung.
- T c. red blood cell count.
- T d. pulmonary ventilation.
- F e. arterial PO_2

Q. 50. **The ventilation-perfusion ratio**
- T a. is increased by hemorrhage.
- T b. is about 0.8
- T c. is more in apex than in base of the lungs in erect posture.
- F d. decreases with increased physiological dead space.
- F e. is decreased in exercise.

Q. 51. **The residual volume is**
- T a. responsible for expansion of the lungs.
- T b. the gas remaining in the lungs at the end of a full expiration.
- T c. greater on average in men than that in women.
- F d. 2000 ml on average in young adult.
- F e. measured directly using a spirometer.

Q. 52. **The approximate amount of gas left in the lungs after maximal forced expiration in a normal woman is**
- T a. 1.1 litre
- F b. 0 litre
- F c. 0.1 litre
- F d. 3.1 litre
- F e. 4.2 litre.

Q. 53. **Functional residual capacity in a male is :**
- T a. 2.2 litres
- F b. 3.8 litres
- F c. 3.3 litres
- F d. 2.8 litres
- F e. 1.2 litres

Q. 54. **Normal functional residual capacity is**
- T a. 2.2 litres
- F b. 0.5 litres

F c. 1.5 litres
F d. 4.0 litres
F e. 1.2 litres

Q. 55. **In advanced age, there is usually a decrease in**
T a. FEV_1
T b. lung elasticity.
T c. resting arterial blood PO_2
F d. residual volume of the lungs.
F e. ratio of lung residual volume to vital capacity.

Q. 56. **Vital capacity is**
T a. TV + IRV + ERV
F b. Tidal volume + Expiratory rserve volume
F c. Tidal volume + inspiratory reserve volume
F d. IRV + ERV
F e. Tidal volume.

Q. 57. **Vital capacity is a measure of**
T a. Tidal volume plus inspiratory reserve volume plus expiratory reserve volume
F b. Tidal volume
F c. Lnspiratory reserve volume plus expiratory reserve volume
F d. Expiratory reserve volume plus reserve volume
F e. None.

Q. 58. **Total vital capacity is decreased but timed vital capacity is normal in**
T a. Scoliosis
F b. Bronchial Asthma
F c. Chronicbronchitis
F d. All the above
F e. None.

Q. 59. **Vital capacity depends on**
T a. Respiratory muscular stregnth
T b. Condition of air way passage
T c. Position of the body
F d. Atmospheric air
F e. Alveolar air.

Q. 60. **Factors mainly responsible for vital capacity are**
T a. air way resistance
T b. strength of respiratory muscle.
T c. elastic recoil tendency of the lungs.
F d. age.
F e. posture.

Q. 61. **Which tends to decrease with increasing age**
T a. Vital capacity
F b. Systolic blood pressure
F c. Pulse pressure
F d. Residual volume
F e. None.

Q. 62. **Which of the following tend to increase in old age**
T a. Residual volume
T b. Systolic BP
T c. Pulse pressure
F d. Vital capacity
F e. All.

Q. 63. **All of following tend to increase in old age except**
F a. Residual volume
F b. Systolic BP
F c. Pulse pressure
F d. None.
T e. Vital capacity

Q. 64. **The instrument used for measuring the vital capacity and FEV is**
T b. Vitalograph
F a. Wright peak flow meter
F c. Carlens catheter
F d. None of the above
F e. All.

Q. 65. **Spirometry measures all of the following except**
F a. Tidal volume
F b. Vital capacity
F c. FEV_1
F e. All
T d. None of the above

Q. 66. **Which of the respiratory volumes cannot be measured by a simple spirometer?**
T a. Functional residual capacity
F b. Vital capacity
F c. Expiratory reserve volume
F d. Inspiratory capacity
F e. Tidal volume

Q. 67. **Spirometer can measure**
T a. Tidal volume
T b. Vital capacity
F c. Expiratory reserve volume
F d. Residual volume
F e. None of the above

Q. 68. **Spirometer cannot measure**
T a. Residual volume
F b. Tidal volume
F c. Vital capacity
F d. Expiratory reserve volume
F e. None of the above

Q. 69. **Closing volume of lung determines**
T a. Small air way resistance
F b. Distensibility of lung
F c. Residual volume
F d. Dead space

F e. None of the above

Q. 70. **Maximum voluntary ventillation (L/min) is**

T a. 210-250
F b. 90-120
F c. 125-170
F d. 170-210
F e. 110-150

Q. 71. **Flow during last stage of expiration decreases because of**

T b. Dynamic compression of airways
F a. Braking by inspiratory muscles
F c. Collapse of alveoli
F d. All
F e. None.

Q. 72. **Total lung capacity is**

T a. 4 - 5 litres
F b. 3 - 4 litres
F c. 6 - 7 litres
F d. 7 - 8 litres
F e. 2 - 3 litres

Q. 73. **Total lung capacity depend on-**

T a. Lung compliance
F b. Size of airway
F c. Closing tidal volume
F d. Residual volume
F e. None.

Q. 74. **Nitrogen washout method used for**

T b. Residual volume
F a. Dead space volume
F c. Tidal volume
F d. All of the above
F d. None of the above.

Q. 75. **The most important substance controlling alveolar ventilation**

T a. CO_2
F b. O_2
F c. H_2O
F d. None of the above
F e. All of the above

Q. 76. **Normal value of FEV_1 in an adult male is**

T a. 80%
F b. 95%
F c. 65%
F d. 55%
F e. 50%

Transport of O_2 & CO_2

Q. 77. **Transport of gases through respiratory membrane is**

T a. simple diffusion.
F b. facilitated diffusion.
F c. osmosis.
F d. active transport.
F e. filtration.

Q. 78. **Factors that affect the net rate of gas diffusion through respiratory membrane are**

T a. pressure difference across the membrane.
T b. cross sectional area of the membrane.
T c. distance through which the gas must diffuse
T d. molecular weight of the gas.
F e. solubility of the gas.

Q. 79. **Diffusion coefficient for different gases in respiration are**

T a. carbondioxide : 20.3
T b. carbon monoxide : 0.81
T c. nitrogen : 0.53
T d. helium : 0.95
F e. oxygen : 2.0

Q.80. **In which of the following diseases would you expect to find an increase in thickness of the respiratory membrane?**

T a. Pulmonary edema
F b. Emphysema
F c. Asthma
F d. Pulmonary artery thrombosis
F e. Skeletal abnormalities of the chest

Q. 81. **Structure through which O_2 must diffuse in passing from alveolar lumen to haemoglobin**

T a. Surfactant containing liquid
T b. Alveolar membrane, basement membrane
T c. Capillary endothelium, plasma and RBC membrane
T d. All of the above
T d. None of the above

Q. 82. **Lung diffusion capacity is measured with**

T a. CO
F b. CO_2
F c. O_2
F d. H_2
F e. H_2O.

Q. 83. **Partial pressures of respiratory gases in alveolor air are**

T a. PCO_2 : 40 mm of Hg
T b. PH_2O : 47 mm of Hg

T c. PN_2 : 569 mm of Hg
F d. PO_2 : 90 mm of Hg
F e. total alveolar pressure : 700 mm of Hg.

Q. 84. **Partial pressure of O_2**
T a. in lung alveoli : 104 mm of Hg.
T b. in aorta : 95 mm of Hg.
T c. arterial end of tissue capillary : 95 mm Hg
T d. venous end of tissue capillany : 40 mm Hg
F e. in cell : 40 mm of Hg.

Q. 85. **Atmospheric pressure (at sea level) is**
T a. 760 mm of Hg
F b. 500 mm of Hg
F c. 770 mm of Hg
F d. 790 mm of Hg
F e. 750 mm of Hg

Q. 86. **PO_2 of alveolar air is**
T a. 104 mm of Hg.
F b. 140 mm of Hg
F c. 120 mm of Hg
F d. 105 mm of Hg
F e. 110 mm of Hg

Q. 87. **The Alveolar PO_2 is**
T a. 104 mm of Hg
F b. 110 mm of Hg
F c. 120 mm of Hg
F d. 150 mm of Hg
F e. 85 mm of Hg

Q. 88. **Arterial PO_2 is reduced in**
T a. Pulmonary hypoventilation
F b. Anaemia
F c. KCN poisoning
F d. CO poisoning
F e. All of the above.

Q. 89. **On the summit of Mt. Everest, where the barometric pressure is about 250 mm Hg, the PO_2 is about**
T a. 50 mmof Hg
F b. 0.1 mm of Hg
F c. 0.5 mm of Hg
F d. 5 mm of Hg
F e. 100 mm of Hg.

Q. 90. **Oxygen toxicity limits exposures to less than ...hours and pressures to .. atmospheres or less respectively:**
T a. 5, 3
F b. 3, 5
F c. 1, 2
F d. 2, 1
F e. 1, 3

Q. 91. **Oxygen affinity decreases in**
T a. Hypoxia
F b. Hypothermia
F c. HbF
F d. Increase in pH
F e. All of the above.

Q. 92. **Decreased O_2 affinity of Hb in blood with decreased pH**
T a. Bhor effect
F b. Haldane effect
F c. Double Haldane effect
F d. Double Bhor effect
F e. All of the above.

Q. 93. **Oxygen affinity is increased by**
T a. Alkalosis
T b. Hypoxia
T c. Increased HbF
F d. Hyperthermia
F e. All of the above

Q. 94. **Increased PO_2 causes**
T a. release of CO_2 due to O_2-haemoglobin formation in the lung.
T b. helps in the entrance of O_2 into the cells.
F c. release of O_2 from blood to the alveolus.
F d. responsible for release of O_2 from the cell.
F e. maintainance of PO_2 in the blood.

Q. 95. **Release of O_2 is increased with**
T a. A fall in tissue PO_2
T b. Any factor which decreases the O_2 affinity for haemoglobin.
T c. An increase in local PCO_2
F d. A decreased temperature
F e. An increase in local pH.

Q. 96. **The state of iron responsible for O_2 transport**
T a. Fe ++
F b. Fe +++
F c. Both
F d. None.
F e. All.

Q. 97. **Arterial O_2 content is reduced in one of following**
T a. Anemic hypoxia
F b. Stagnant hypoxia
F c. Histotoxic hypoxia
F d. Ischemic hypoxia
F e. All.

Q. 98. **Oxygen affinity is increased by**
T a. Alkalosis
T b. Hypoxia
T c. Increased HbF

F d. Hyperthermia
F e. All.

Q. 99. **Carbon monoxide**
T a. has a greater affinity to combine with Hb than does O_2.
T b. can combine with Hb, where O_2 is supposed to bind.
T c. interferes with O_2 transport
F d. loosely combines with CO_2 in the plasma
F e. interferes with CO_2 transport.

Q. 100. **Which of the following diffuses freely from plasma to extracellular space**
T a. CO_2
F b. H_2O
F c. Glucose
F d. Proteins
F e. Amino acid.

Q. 101. **The diffusing capacity for carbon dioxide compared to that for oxygen is**
T a. 20 times
F b. 10 times
F c. 5 times
F d. 15 times
F e. 2 times

Q. 102. **PCO_2 of alveolar air is**
T a. 40 mm of Hg
F b. 104 mm of Hg
F c. 50 mm of Hg
F d. 35 mm of Hg
F e. 45 mm of Hg.

Q. 103. **PCO_2 in venous blood is**
T a. 46 mm of Hg
F b. 40 mm of Hg
F c. 1.3 mm of Hg
F d. 0.3 mm of Hg
F e. 0.7 mm of Hg

Q. 104. **Increased PCO_2 causes**
T a. release of O_2 from Nb
T b. shift of oxhaemoglobin curve to right
F c. shift of oxhaemoglobin curve to left.
F d. release of CO_2
F e. release of H_2

Q. 105. **Increased CO_2 in blood causes**
T a. respiratory acidosis.
T b. raised cerebral blood flow.
T c. raised plasma bicarbonate.
F d. metabolic acidosis.
F e. alkaline urine.

Q. 106. **A rise in arterial PCO_2**
T a. increases cerebral blood flow
T b. increases arterial pressure
T c. increases the plasma bicarbonate level.
T d. causes increased ventilation.
F e. shifts the O_2-Hb dissociation curve to the left.

Q. 107. **Carbon dioxide**
T a. uptake by the blood leads to similar increases in HCO_3^- ion concentration.
T b. stimulates ventilation when breathed at a concentration of 5%.
F c. is canied as carboxyhaernoglobin on the haemoglobin molecule.
F d. uptake by the blood increases its O_2 binding power.
F e. content is greater than O_2 content in arterial blood.

Q. 108. **Carbon dioxide**
T a. Is more soluble than oxygen.
T b. Increases proportionately within body with decreased ventilation.
F c. Can not penetrate the blood brain barrier.
F d. Is irreversibly hydrated by carbonic anbydrase.
F e. Is hydrated before crossing red cell membrane

Q. 109. **CO_2 transport in the blood**
T a. Occurs mainly in the form of HCO_3^-
T b. Is promoted by carbonic anhydrase within the erythrocytes.
F c. Is saturated at a PCO_2 of approximately 6 kpa.
F d. Is promoted by an increase in the O_2 cotent of the blood.
F e. Leads to an increase in plasma Cl^- level.

Q. 110. **CO_2 transported in the blood is**
T a. In carbamino compounds
T b. In dissolved form in plasma
T c. In HCO_3- form
F d. Bound to Cl^-
F e. In carboxyhemoglobin form.

Q. 111. **Most of the CO_2 transported in the blood is**
T a. In HCO_3^-.
F b. In dissolved state
F c. As carbamino compounds formed from plasma proteins.
F d. As carbamino compounds formed from haemoglobin.
F e. In bound form with Cl ion.

Q. 112. **In a normal adult, 24 hour production of CO_2 is about :**
T a. 280 L
F b. 150 L
F c. 330 L

F d. 410 L
F e. 180 L

Q. 113. **In sternuous exercise, PCO_2 (mm of Hg) falls from:**
T a. 40 to 15
F b. 60 to 35
F c. 25 to 10
F d. 35 to 0
F e. 15 to 10

Q. 114. **CO_2 is carried in the blood**
T a. In combination with haemoglobin
T b. In physical solution in plasma
T c. In combination with plasma proteins
T d. Mainly as bicarbonate
F e. None.

Q. 115. **The most importatnt factor in transport of CO_2 as bicarbonate is**
T a. Carbonic anhydrase in RBC
F b. Affinity to Hb
F c. Basic nature of HCO_3
F d. Increased solubility of CO_2
F e. None.

Q. 116. **P_{50} is**
T a. 28-32 mm of Hg.
T b. partial pressure of O_2 at which 50% haemoglobin statura tion occurs.
F c. 40-50 mm of Hg.
F d. 50% haemoglobin staturation with O_2
F e. an indicator of PCO_2

Q. 117. **At high altitude, there is an increase in**
T a. arterial pH.
T b. diffusing capacity of the lung.
T c. red blood cell count.
T d. pulmonary ventilation.
F e. arterial PO_2

Q. 118. **All are true about 2,3 DPG**
T a. High levels in red cells.
T b. Low affinity of O_2 to hemoglobin
T c. Altered binding to fetal hemoglobin
F d. Causes Bohr effect
F e. None.

Q. 119. **Role of 2,3 DPG in hemoglobin**
T a. Unloading oxygen to tissues
F b. Increased affinity for oxygen
F c. Buffering capacity
F d. Osmotic fragility.
F e. None.

Q. 120. **A shift of oxyhaemoglobin dissociation curve to the right**
T a. increases the P_{50}.
T b. occurs if blood temperature rises
T c. favours O_2 delivery to the tissues.
F d. favouis O_2 up take from the lung by alveolar capillary blood
F e. occurs in the pulmonary capillaries

Q. 121. **Oxyhemoglobin dissociation curve is shifted to the right by**
T a. increased 2,3 DPG
T b. increased PCO_2
F c. increased pH
F d. decreased temperature.
F e. increased PO_2

Q. 122. **Oxyhemoglobin dissociation curve is shifted to the left by**
T a. decreased 2,3 DPG
T b. increased pH
T c. fetal haemoglobin.
T d. increased PO_2
F e. increased PCO_2

Q. 123. **Factors affecting oxy-hemoglobin dissociation curve are**
T a. H^+ concentration.
T b. Temperature.
T c. PCO_2
F d. PN_2
F e. PH_2O

Q. 124. **The O_2-Hb dissociation curve shows that**
T a. O_2 saturation of systemic arterial blood is 97%
T b. O_2 saturation in venous blood is 75%.
T c. flat part indicates oxygenation of Hb in the lungs
T d. it is sigmoid in shape.
F e. flat part occurs in the tissues capillaries.

Q. 125. **Oxygen dissociation is increased by**
T a. Hypercapnia
T b. 2,3 DPG increase
T c. Increased temperatures
F d. Metabolic alkalosis
F e. All.

Q. 126. **Oxygen dissociation curve is**
T a. S-shaped
F b. Bell shaped
F c. Normal curve type
F d. Delta shaped
F e. None.

Q. 127. **Oxygen dissociation is increased by**
T a. Hypercapnia

T b. 2,3 DPG increase
T c. Increased temperatures
F d. Metabolic alkalosis
F e. All.

Q. 128. **Oxygen dissociation curve is shifted to the right in**
T a. Fall in pH
T b. Rise in temperature
T c. Increase of 2,3 DPG
F d. Hb F
F e. All.

Q. 129. **Shift to right of O_2 dissociation curve is seen in**
T a. Decreased pH
F b. Increase Pa CO_2
F c. Decreased Pa CO_2
F d. Increased pH
F e. None.

Q. 130. **Haemoglobin unlike myoglobin shows**
T a. Parabolic curve of oxygen association
F b. Positive cooperativity
F c. Cooperative index of 81
F d. Hill's coefficient of 1
F e. None.

Q. 131. **Nernst equation deals with**
T a. Chloride shift
F b. Oxygen uptake
F c. Cellular ATP levels
F d. Plasma bicarbonate level
F e. All.

Q. 132. **In Bohr effect**
T a. O_2 dissociation increases in hypoxia
F b. O_2 dissociation decreases in hypoxia
F c. O_2 dissociation increase with elevated temperature
F d. None.
F e. All of the above

Regulation of Respiration

Q. 133. **The primary stimulus for respiration is a**
T a. Two fold increase in the PCO_2 of inspired air.
F b. Two fold increase in the PO_2 of inspired air
F c. 50% decrease in the PCO_2 of inspired air
F d. 50% increase in the PO_2 of inspired air
F e. 50% decrease in PCO_2 in inspired air.

Q. 134. **Most potent respiratory stimulant is**
T a. Carbondioxide
F b. Oxygen
F c. H^+
F d. K^+
F c. N_2

Q. 135. **The most important substance controlling alveolar ventilation**
T a. CO_2
F b. O_2
F c. H_2O
F d. None of the above
F e. All of the above

Q. 136. **Spontaneous respiration ceases after**
T a. Transection of the brain stem at the
F b. Transection of the brain stem above the pons caudal end of the medulla.
F c. Bilateral vagotomy.
F d. Bilateral vagotomy combined with transection of the brain stem at the superior border of the pons.
F e. Transection of the spinal cord at the level of first thoracic segment.

Q. 137. **J receptor when stimulated causes**
T a. Rise in the frequency of breathing.
T b. Decrease in the depth of inspiration.
F c. Increase in the depth of inspriation.
F d. Fall in the frequency of breathing. acidosis.
F e. Acidosis.

Q. 138. **The main respiratory control neurons**
T a. Send out regular bursts of impulses to inspiraory muscles during qutie respiration.
F b. Send out regular burst of impulses to expiratory muscles during quite respiration.
F c. Are unaffected by the stimulation of pain receptors.
F d. Are located in the pons.
F e. are unaffected by impulses from the cerebral cortex.

Q. 139. **Respiratory centre is composed of**
T a. pneumotaxic center
T b. apneustic center.
T c. Dorsal respiratory group of neuron
T d. ventral respiratory group of neuron
F e. chemotaxic center

Q. 140. **What is not true for respiration centre?**
T a. Sends out regular impulses to expiratory
F b. Situated in the medulla and pons
F c. Sends out regular bursts of impulses to expiratory muscles during quiet respiration muscles during quiet respiration
F d. Is inhibited during swallowing and vomitting
F e. All.

Q. 141. **Stimulation of the proximal end of a cut vagus would be expected to**
T a. inhibit respiration
T b. cause apnea.
F c. increase heart rate

F d. inhibit coughing
F e. raise blood pressure

Q. 142. **Destruction of the pneumotaxic center located in the pons can cause**
T a. Apneustic respiration
F b. Forcefull expiration
F c. accelerated respiration
F d. Apnea
F e. Cheyne-Stokes breathing.

Q. 143. **CO_2 affects respiratory centre via**
T a. CSF H^+ concentration
F b. Carotid body
F c. Inflation and deflation receptors
F d. Aortic body
F e. All.

Q. 144. **What happens when CO_2 in inspired air increases beyond 10% at atmospheric pressure?**
T a. Depression of CNS
T b. Decreased ventilation
T c. Diminished sensory acuity
T d. Confusion, coma and death
T e. All.

Q. 145. **Respiration is stimulated by**
T a. decreased pH of the blood.
T b. decreased concentration of O_2 in the blood.
T c. excess carbondioxide in the blood.
T d. excess hydrogen ions in the blood.
F e. decreased CO_2 in the blood.

Q. 146. **The factors that increase the rate and depth of respiration during exercise are**
T a. direct stimulation of respiratory centre from motor cortex.
T b. indirect stimulation from proprioceptors.
T c. increased PCO_2 stimulating respiratory centre
T d. decreased PO_2 stfmulating respiratory centre.
F e. increased pH stimulating respiratory centre

Q. 147. **Variations in concentration of which of the following component of blood or cerebrospinal fluid do not affect respiration are**
T a. arterial Na^+
F b. arterial HCO_3^-
F c. arterial H^+
F d. ceroborospinal fluid CO_2
F e. ceroborospinal fluid H^+.

Q. 148. **Chemorceptors**
T a. Stimulates ventilation when the arterial PCO_2 increases by 10%
T b. Can lead to an increase in ventilation when the arterial pH falls
T c. In the brain are responsible for the change in arterial PCO_2.
F d. Stimulate ventilation when the arterial PO_2 falls by 10%
F e. In the carotid body provide the main drive to ventila tion under normal circumstances

Q. 149. **The following stimulate the peripheral chemo-receptors**
T a. Hypoxia
T b. Acidosis
T c. Low perfusion pressure.
F d. Hypocapnia
F e. None.

Q. 150. **Chemoreceptor mechanism is not triggered in**
T a. Histotoxic hypoxia.
F b. Anemic hypoxia
F c. Hypoxic hypoxia
F d. Stagnant hypoxia
F e. None.

Q. 151. **In moderate exercise stimulation of respiration is due to**
T a. Joint propioception receptor
F b. Stimulation of J receptor
F c. Stimulation or lung receptor
F d. Stimulation of medullary centre
F e. None.

Q. 152. **All are increased during exercise**
T a. Cardiac output
T b. Venous return
T c. Coronary blood flow
F d. Peripheral vascular resistance
F e. None.

Q. 153. **Moderate exercise tachypnea is due to stimulation of which receptor**
T a. Propioception
F b. J receptor
F c. Lung receptor
F d. Baro-receptor
F e. None.

Q. 154. **At high altitude, there is an increase in**
T a. arterial pH.
T b. diffusing capacity of the lung.
T c. red blood cell count.
T d. pulmonary ventilation.
F e. arterial PO_2

Q. 155. **First compensatory mechanism in high altitude sickness is**
T a. Polycythemia
T b. Hyperventilation

F c. Alkaline urine
F d. Anaemia
F e. Hypoventilation.

Q. 156. **An increase in ventilation occurs in**
T a. Fall in plasma bicarbonate
T b. Fall in pH of CSF
T c. Rise in blood adrenaline level
F d. Sleep
F e. All.

Q. 157. **J receptor stimulation causes**
T a. Apnoea
F b. Tachynoea
F c. Tachycardia
F d. Hypotension
F e. None.

Q. 158. **Which occurs after hyperventillation with 6% CO_2**
T a. Apnea
F b. Continued hyperventilation
F c. Cheyne stoke's breathing
F d. None.
F e. Kussmaul's breathing

Applied

Q. 159. **In heavy exercise extra O_2 is supplied by**
T a. Increased PCO_2.
T b. Linear flow
T c. Open patent arteries
T d. Increased diffusing area
F e. Increased PO_2

Q. 160. **During heavy exercise there are**
T a. Increased metabolic activity
T b. Increased H^+ concetration.
T c. Increased PO_2 concetration.
F d. Decreased PCO_2
F e. Decreased O_2 concetration.

Q. 161. **Cyanosis**
T a. occurs in polycythemic patient.
T b. occurs when reduced Hb is more than 5 gm/dl.
T c. is caused by high level of methhaemoglobin in the blood.
F d. occurs in anaemic patient.
F e. is caused by high level of carboxy haemoglobin in the blood

Q. 162. **Cyanosis is seen if the concentration of methaemoglobin is more than**
T a. 1.5 G%
F b. 2.0 G%
F c. 3.0 G%
F d. 4.0 G%
F e. 5.0 G%

Q. 163. **Obstructive airway disease reduces**
T a. peak expiratory flow rate.
T b. vital capacity
T c. the forced expiratory volume in first second (FEV_1)
F d. the ratio of FEV_1 and VC
F e. residual volume

Q. 164. **In emphysema there are**
T a. abnormal ventilation perfusion ratio.
T b. decreased diffusing capicity.
F c. normal removal of CO_2.
F d. decreased pulmonary vascular resistance.
F e. Increased airway resistance.

Q. 165. **Hypoxia causes**
T a. Headache
T b. Drowsiness
T c. Loss of self control
F d. Decreased heart rate
F e. Decreased RBC count.

Q. 166. **Hypoxia in chronic respiratory failure**
T a. leads to increased formation of erythropoietin
T b. causes pulmonary hypertension.
T c. may lead to right heart failure.
T d. may cause central cyanosis.
F e. may cause peripheral cyanosis.

Q. 167. **In histotoxic hypoxia**
T a. PO_2 is normal in arterial blood.
T b. O_2 from the capillary blood is not extracted any more
T c. PO_2 of venous blood remains high
F d. PCO_2 of venous blood remains high
F e. O_2 content of the blood is low

Q. 168. **In anemic hypoxia**
T a. haemoglobin concentration is reduced.
T b. arterial PO_2 is normal.
T c. decreased PCO_2 in the arterial blood occurs.
F d. decreased PO_2 in arterial blood occurs.
F e. increased 2,3-DPG in the blood is present.

Q. 169. **If the hypoxia is of slower onset, compensatory mechanisms are**
T a. Hyperventilation
T b. Alkalosis.
T c. Polycythenna.
F d. Acidosis.
F e. Hypoventilation.

Q. 170. **The most common form of hypoxia is :**
T a. Hypoxic

F b. Stagnant
F c. Anemic
F d. Histotoxic
F e. None.

Q. 171. **Hypoxia causes vasoconstriction in**
T a. Lungs
F b. Muscle
F c. Liver
F d. Spleen
F e. None.

Q. 172. **All the following type of hypoxia stimulate the peripheral chemoreceptor, except**
T a. Histotoxic hypoxia
F b. Anaemic hypoxia
F c. Stagnant hypoxia
F d. Hypoxic hypoxia
F e. None

Q. 173. **Which of the following type of hypoxia stimulate the peripheral chemoreceptor**
T a. Anaemic hypoxia
T b. Stagnant hypoxia
T c. Hypoxic hypoxia
F d. Histotoxic hypoxia
F e. All.

Q. 174. **Severe hypoxia may produce:**
T a. BP rise
F b. BP fall
F c. Fall followed by BP rise
F d. No change
F e. None

Q. 175. **Hypoxia is characterised by**
T a. Low arterial PO_2
T b. Intense chemoreceptor response
T c. Favourable response to 100% oxygen
T d. All of the above
F e. None

Q. 176. **Arterial O_2 content is reduced in one of following**
T b. Anemic hypoxia
F a. Stagnant hypoxia
F c. Histotoxic hypoxia
F d. Ischemic hypoxia
F e. None.

Q. 177. **Hyperboric oxygenation is useful in**
T a. Congenital heart disease
T b. Gas gangrene
T c. Carbon-monoxide poisoning
F d. Nitrogen toxicity
F e. All.

Q. 178. **Oxygen therapy is not effective in**
T a. Histotoxic hypoxia
F b. Hypoxic hypoxia
F c. Anaemic hypoxia
F d. Ischemic hypoxia
F e. None.

Q. 179. **Oxygen therapy is effective in**
T a. Hypoxic hypoxia
T b. Anaemic hypoxia
T c. Ischemic hypoxia
F d. Histotoxic hypoxia
F e. All.

Q. 180. **In eupnoea there is**
T a. normal rate or depth of breathing
F b. decreased alveolar ventilation
F c. rapid shallow breathing
F d. difficulty in breathing
F e. decreased rate of breathing.

Q. 181. **Stimulation of the proximal end of a cut vagus would be expected to**
T a. inhibit respiration
T b. cause apnea.
F c. increase heart rate
F d. inhibit coughing
F e. raise blood pressure

Q. 182. **Cheyne-Stokes breathing is**
T a. slowly waxing and waning respiration.
T b. most common type of periodic breathing.
F c. due to acute asthma.
F d. normal breathing.
F e. due to high altitude.

Q. 183. **Periodic breathipg**
T a. is characterised by deep breathing for short period followed by shallow or absence of breathing.
T b. is abnormal respiration.
T c. occurs during sleep.
F d. is normal respiration.
F e. is caused occastionally due to tuberculosis.

Q. 184. **Apneusis**
T a. occurs due to lesion through midpons and vagus nerve.
T b. is ceassation of breathing at the inspiration.
F c. is ceassation of breathing at the height of expiration.
F d. is temporary ceassation of breathing.
F e. occurs in periodic breathing.

Q. 185. **CO_2 retention is most likely to occur in**
T a. Ventilatory failure
F b. High mountain

F c. Carbon monoxide poisoning
F d. Pulmunary failure
F e. Hysterical hyperventilation.

Q. 186. **Pulmonary fibrosis would be expected to produce**
T a. Cyanosis
F b. Histotoxic hypoxia
F c. Stagnant hypoxia
F d. Decreased vital capacity
F e. Emphysema.

Q. 187. **Chronic cigarette smoking produces**
T a. Increased carbmonoxyhemoglobin in blood.
T b. Patches of atelectasis
T c. Myocardial ischemia.
T d. Loss of elastic tissue in the lung
F e. increased anatomic dead space

Q. 188. **O_2 delivery to the tissue would be reduced to the greatest extent in**
T a. a patient with carbon monoxide poisoning
F b. A normal subject breathing 100% O_2 on the top of Mt. everest
F c. A normal subjcet running a marathon at sea level.
F d. a person who has ingested cyanide
F e. a patient with moderately severe metabolic acidosis.

Q. 189. **Manifestations of oxygen toxicity are**
T a. Irritation of the respiratory tract
T b. Retrolental fibroplasia
T c. Convulsions
T d. Cystic lungs in infants
F e. Rupture of the alevoli.

Q. 190. **The poison cyanide inhibits the reaction between**
T a. Cytochrome oxidase and molecular oxygen
F b. Cytochrome A and Cytochrome B
F c. Phosphofructokinase and glucose oxidase
F d. Haemoglobin and oxyhaemoglobin
F e. None.

Q. 191. **Death due to cyanide poisoning results from which of the following types of anoxia?**
F a. Anoxic anoxia
F b. Anaemic anoxia
F c. Stagnant anoxta
F d. Histotoxic anoxia
T e. None of the above.

Q. 192. **Cyanide posoning affects ..... function**
T a. Respiratory
F b. Cardiac
F c. Renal
F d. Liver
F e. None.

Q. 193. **Earliest change in high altitude is**
T a. Hyperventillation
F b. Decrease in work capacity
F c. Drowsiness
F d. Polycythemia
F e. None.

Q. 194. **A person ascends to 12,000 feet develops acute breathlessness this is due to**
T a. Carbon dioxide washout
F b. Decreased pulmonary blood flow
F c. Decreased hypoxic stimulation of respiration
F d. Mechanical interference of thorax
F e. None.

Q. 195. **Which of the following occur in high altitude acclimatisation**
T a. Reticulocytosis
T b. Increase serum erythropoletin
T c. Increased serum cortisol
F d. Increased blood glucose
F e. All.

Q. 196. **Which is seen in high altitude**
T a. Respiratory alkalosis
F b. Metabolic alkalosis
F c. Respiratory acidosis
F d. Metabolic acidosis
F e. None.

Q. 197. **Alkalosis accurs whenever pH is above**
T d. 7.40
F a. 7.000
F b. 7.24
F c. 7.36
F e. 6.40

Q. 198. **Metabolic alkalosis associated with prolonged vomiting is due to primarily to loss of**
T a. Chloride
F b. Sodium
F c. Potassium
F d. Hydrogen ion
F e. None.

Q. 199. **Metabolic alkalosis is seen in**
T a. Thiazide diuretics
T b. Prolonged vomiting
T c. Systemic antacid therapy
F d. Ureterosigmoidostomy
F e. All.

Q. 200. **In hypercapnic acidosis**
T a. Cerebral vasodiliation can occur
T b. Plasma bicarbonate rises
T c. May be associated with pickwickian syndrome

F d. Kaussmal breathing may be present
F e. All.

Q. 201. **Respiratory acidosis can cause**
T a. Increased PCO_2 and decreased P^H
F b. Decreased PCO_2 and decreased P^H
F c. Increased PCO_2 and increased P^H
F d. Decreased PCO_2 and increased P^H
F e. None.

Q. 202. **Smoking causes**
T a. Ciliary motility
T b. Cellular hyperplasia
T c. Mucous secretion
T d. All of the above
F e. None.

Q. 203. **In cigarette smoking, surfactant is :**
T a. Decreased
F b. Increased
F c. Increased followed decrease
F d. Unaltered
F c. Decreased followed increase.

Q. 204. **Destruction of lung tissue and defective gaseous exchange causes**
T d. Pulmonary hypertension
T c. Increased red cell number
T a. Prominent P wave
F b. Decreased cerebral blood circulation
F e. None.

Q. 205. **In COPD all are affected**
T a. FEV
T b. Ratio of FEV to vital capacity
T c. None.
F d. FVC
F e. None.

Endocrinology

Endocrinology

Endo = Internal and crinos = Secretion.

Endocrinology is a branch of medical science which deals with the study of different endocrine glands of the body.

Endocrine gland : Means ductless gland which directly poured their secretion into the blood.

Endocrine glands are :

1. Hypothalamus (neuroendocrine gland)
2. Pituitary (master gland) gland
   a. Anterior pituitary gland
   b. Posterior pituitary gland
3. Thyroid gland.
4. Parathyroid glands
5. Adrenal glands
   a. Adrenal cortex
   b. Adrenal medulla
6. Pancrease (Endocrine portion Islets of Langerhans)
7. Testis (in case of male)
8. Ovaries (in case of female)
9. Placenta (during pregnancy).

(Ref. Guyton & Hall-11th ed; Page 906)

Coordination of the body functions by chemical messengers

The multiple activities of the cells, tissues, and organs of the body are coordinated by the interplay of several types of communication systems, including :

1. *Neural*, in which chemicals (neurotransmitters) are released at synaptic junctions and act locally to control cell function
2. *Endocrine*, in which glands or specialized cells release into the circulating blood chemicals (hormones) that infuence the function of cells at another location in the body
3. *Neuroendocrine*, in which neurons secrete substances : (neurohormones) that reach the circulating blood and influence the function of cells at another location in the body
4. *Paracrine*, in which cells secrete substances that diffuse in to the extracellular fluid and affect neighboring cells
5. *Autocine*, in which a cell secretes substances that affect the function of the same cell by binding to the cell surface receptors.

For example, the adrenal medullae and the pituitary gland secrete their hormones primarily in response to neural stimuli. The neuroendocrine cells, located in the hypothalamus, have axons that terminate in the posterior pituitary gland and median eminence and secrete several neurohormones, including *antidiuretic hormone (ADH)*, *oxytocin*, and *hypophysiotropic hormones*, that control the secretion of anterior pituitary hormones.

The endocrine hormones are carried by the circulatory system to cells throughout the body, including the nervous system in some cases, where they bind with receptors and initiate many reactions. Some endocrine hormones affect most cells of the body; for example, *growth hormone* (from the anterior pituitary gland) causes growth in most parts of the body, and *thyroxine* (from the thyroid gland) increases the rate of many chemical reactions in almost all the body's cells.

Other hormones affect only specific tissues called *target tissues*, because only these tissues have receptors for the hormone. For example, *adrenocorticotropic hormone (ACTH)* from the anterior pituitary gland specifically stimulates the adrenal cortex, causing it to secrete adrenocortical hormones, and the *ovarian hormones* have specific effects on the female sex organs as well as on the secondary sexual characteristics of the female body.

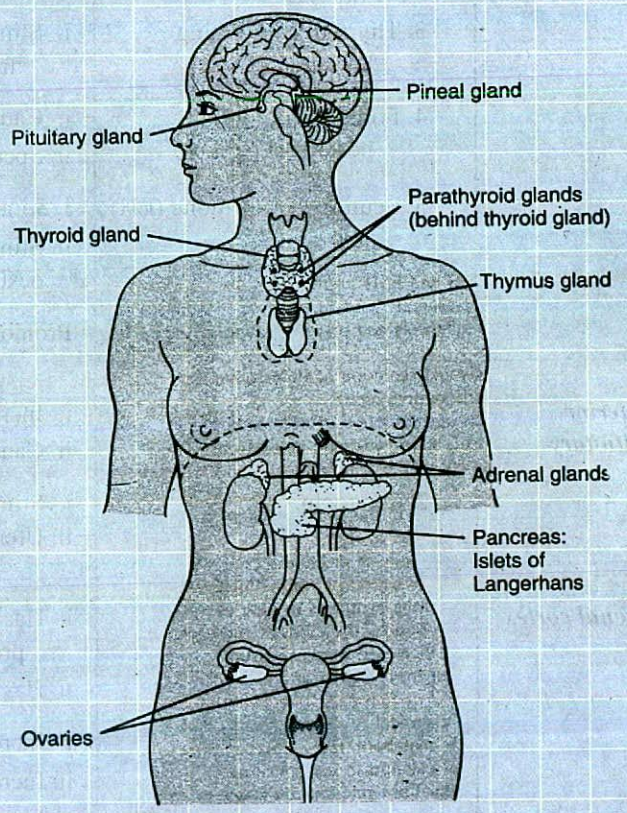


Fig. 8-1. *Anatomical loci of the major endocrine glands of the body except the placenta and testes.*

Figure shows the anatomical loci of the major endocrine glands of the body except the placenta and testes, which are additional sources of the sex hormones, and the kidneys, provides an overview of the different hormone systems and their most important actions.

(Ref. Guyton & Hall-11th ed; Page 905)

Endocrine glands, Hormones and their important functions and structure :

Gland	*Name of the Hormone*	*Major functions*	*Structure*
Hypothalamus	Thyrotropin-releasing hormone (TRH)	i. Stimulates secretion of TSH and prolactin	Peptide
	Corticotropin-releasing hormone (CRH)	i. Causes release of ACTH	Peptide
	Growth hormone-releasing hormone (GHRH)	i. Causes release of growth hormone	Peptide
	Growth hormone-inhibitory hormone (GHRH) (somatostatin)	i. Inhibits release of growth hormone	Peptide
	Gonadotropin-releasing hormone (GnRH)	i. Causes release of LH and FSH	
	Dopamine or prolactin inhibiting factor (PIF)	i. Inhibit release of prolactin	Amine
Anterior Pituitary	1. Growth hormone	i. Stimulates protein synthesis and ii. Overall growth of most cells and tissues.	Peptide
	2. Adrenocorticotropic hormone (ACTH)	i. Stimulate the adrenal cortex to secrete adrenocortical hormone.	Peptide
	3. Thyroid stimulating hormone (TSH)	i. Stimulate synthesis and secretion of thyroxine and tri-iodothyronine.	Peptide
	4. Follicle stimulating hormone (FSH).	i. Causes growth of follicle in the ovaries and ii. Sperm maturation in Sertoli cells of testes.	Peptide
	5. Leutinizing hormone (LH)	i. Stimulates testosterone synthesis in Leyding cells of testes; ii. Stimulates ovulation, formation of corpus luteum, and oestrogen and progesteron synthesis in ovaries.	Peptide
	6. Prolactin	Promotes development of the breasts and secretion of milk.	Peptide
Posterior Pituitary	1. Antidiuretic hormone (ADH, Also called vasopressin)	i. Increases water reabsorption by the kidneys and ii. Causes vasoconstriction and increased blood pressure.	Peptide
	2. Oxytocin.	i. Stimulates milk ejection from breasts and ii. Uterine contraction.	Peptide
Adrenal cortex	1. Cortisol	i. Has multiple metabolic functions for controling metabolism of proteins, carbohydrates and fats. ii. Has anti-inflammatory effects.	Steriod
	2. Aldosterone	i. Increases renal sodium reabsorption ii. Increases renal potassium secretion iii. Increases renal hydrogen ion secretion	Steriod
Thyroid	1. Thyroxine (T_4) & triidothyronine (T_3)	i. Increase the rates of chemical reactions in most cells. ii. Thus increasing body metabolc rate.	Amine
	2. Calcitonin.	i. Promotes the deposition of Ca^{++} in the bones. ii. Decreases the extracellular Ca^{++} concentration.	Peptide

(Ref. Guyton & Hall-11th edition; Page 907)

Endocrine glands, Hormones and Their Important Functions and Structure :

Gland	*Name of the Hormone*	*Major functions*	*Structure*
Parathyroid	1. Parathyroid hormone (PTH)	i. Controls serum Ca^{++} concentration by increasing calcium absorption by the gut (GIT) and kidneys and release calcium from the bones.	Peptide
Pancrease Islets of Langerhans	1. Insulin (β cells)	i. Promotes glucose entry in many cells and in this way controls carbohydrates metabolism.	Peptide
	2. Glucagon (α cells)	i. Increases the synthesis and release of glucose from the liver into the circulating body fluids.	Peptide
Ovaries	1. Estrogens	i. Promote growth and development of the female reproductive system, female breasts and female secondary sexual characteristics.	Steroid
	2. Progesterone	i. Stimulate the secretion of *uterine milk* by the uterine endometrial glands ii. Promote development of the secretory apparatus of the breast.	Steroid
Testes	1. Testosterone	i. Promotes development of male reproductive system and ii. Promotes development of male secondary sexual characteristics.	Steroid
Placenta	1. Human chorionic gonadotropin (HCG)	i. Promotes growth of corpus luteum and secretion of estrogens and progesterone by the corpus luteum.	Peptide
	2. Human somatomammotropin	i. Probably helps promote development of some fetal tissue as well as the mother's breasts.	Peptide
	3. Estrogens	See actions of estrogen from ovaries	Steroid
	4. Progesterone	See actions of progesterone from ovaries	Steroid
Kidney	1. Renin	i. Catalyzes conversion of angiotensinogen to angiotensin I (acts as an enzyme)	Peptide
	2. 1,25 Dihydroxychole-calciferol	i. Increases intestinal absorption of calcium and bone mineralization	Steroid
	3. Erythropoietin	i. Increases erythrocyte production.	Peptide
Heart	1. Atrial natriuretic peptide (ANP)	i. Increases sodium excretion by the kidneys ii. Reduces blood pressure.	Peptide
Stomach	1. Gastrin	i. Stimulates HCl secretion by parietal cells.	Peptide
Small Intestine	1. Secretin	i. Stimulates pancreatic acinar cells to release bicarbonate and water.	Peptide
	2. Cholecystokinin (CCK)	i. Stimulates gallbladder contraction and ii. Release of pancreatic enzymes.	Peptide

(Ref. Guyton & Hall-11th edition; Page 907)

Functions of endocrine glands

The multiple hormone systems of the body play a key role in regulating almost all its functions, including :

i. Metabolism
ii. Growth and development
iii. Water and electrolyte balance
iv. Reproduction
v. Behavior.

* For instance, without growth hormone, a person becomes a dwarf.
* Without thyroxine and triiodothyronine from the thyroid gland, almost all the chemical reactions of the body become sluggish, and the person becomes sluggish as well.
* Without insulin from the pancreas, the body's cells can use little of the food carbohydrates for energy.
* Without the sex hormones, sexual development and sexual functions are absent.

(Ref. Guyton & hall-11th edition; Page 905)

Factor

A substance that has the action of a hormones but that has not been purified and indentified as a distinct chemical compound is called factor.

(Ref. Guyton & Hall-11th edition; Page 905)

Hormone

Hormone is a chemical substance that is secreted into the internal body fluid by one cell or group of cells and exerts a physiological control effect on other cells of the body.

(Ref. Guyton & Hall-11th edition)

Classification of Hormone

a. ***Based on chemical nature*** :

i. *Proteins or polypeptides hormone :* Hormones secreted by the anterior and posterior pituitary gland, the pancreas (insulin and glucagon), the parathyroid gland (parathyroid hormone) and many others.

ii. *Steroid hormones :* Hormones secreted by the adrenal cortex (*cortisol* and *aldosterone*), the ovaries (*estrogen* and *progesterone*), the testes (*testosterone*), the placenta (*estrogen and progesterone*).

iii. *Derivatives of the amino acid tyrosine :* Hormones secreted by the thyroid (thyroxine and triiodothyronine) and the adrenal medullae (epineph- rine and norepinephrine).

There are no known polysaccha- rides or nucleic acid hormones.

(Ref. Guyton & Hall-11th edition; Page 906)

b. ***Based on the site of action*** :

i. *General hormone :* Has a generalized action through out the body e.g growth hormone, thyroid hormone, insulin.

ii. *Local hormone :* Has a localized function upon the local cells e.g Local hormones of GI tract. *(Described in digestive system).*

iii. *Trophic hormone :* Hormones which are secreted from an endocrine gland and acts upon another gland and produce their secretion, called trophic hormone. e.g TSH, ACTH, LH etc.

Synthesis and storage of hormones

1. ***Polypeptide and protein hormones*** *are stored in secretory vesicles until needed* : Most of the hormones in the body are polypeptides and proteins. These hormones range in size from small peptides with as few as three amino acids (*thyrotropin-releasing hormone*) to proteins almost 200 amino acids long (*growth hormone* and *prolactin*). In general, polypeptides with 100 or more amino acids are called *proteins*, and those with fewer that 100 amino acids are referred to as *peptides*.

Protein and peptide hormones are synthesized on the rough end of the endoplasmic reticulum of the different endocrine cells in the same fashion as most other proteins (Figure 8-2). They are usually synthesized first as larger proteins that are

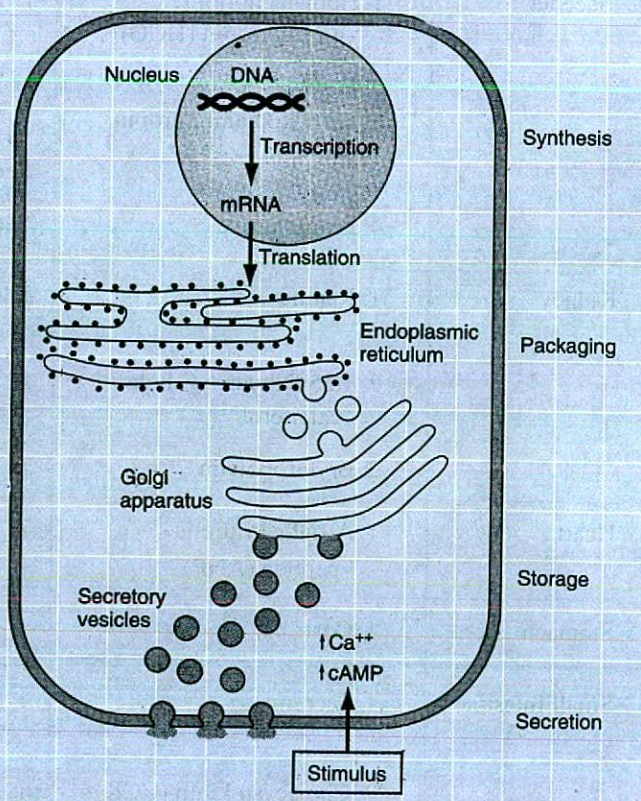


Fig. 8-2. *Synthesis and secretion of peptide hormones. The stimulus for hormone secretion often involves increased intracellular calcium or decreased cAMP in the cell.*

not biologically active (*prepro- hormones*) and are cleaved to form smaller *prohormones* in the endoplasmic reticulum. These are then transferred to the Golgi apparatus for packaging into secretory vesicles. In this process, enzymes in the vesicles cleave the *prohomones* to produce smaller, biologically active *hormones* and *inactive fragments*. The vesicles are stored within the cytoplasm, and many are bound the cell membrane until their secretion is needed. Secretion of the hormones (as well as the inactive fragments) occurs when the secretory vesicles fuse with the cell membrane and the granular contents are extruded into the interstitial fluid or directly into the bloood stream by *exocytosis*.

In many cases, the stimulus for exocytosis is an incrase in cytosolic calcium concentration caused by depolarization of the plasma membrane. In other instances, stimulation of an endocrine cell surface receptor causes increased cyclic adenosine monophosphate (*cAMP*) and subsequently activation of protein kinases that initiate secretion of the hormone. The peptide hormones are water soluble, allowing them to enter the circulatory system easily and be carried to their target tissues.

(Ref. Guyton & Hall-11th edition; Page 906)

2. ***Steroid hormones** are usually synthesized from cholesterol and are not stored* : The chemical structure of steroid hormones is similar to cholesterol, and in most instances they are synthesized from cholesterol itself. They are lipid soluble and consist of three cyclohexyl rings and one cyclopentyl ring combined into a single structure. Although there is usually very little hormone storage in steroid-producing endocrine cells, large stores of cholesterol esters in cytoplasm vacuoles can be rapidly mobilized for steroid synthesis after a stimulus. Much of the cholesterol in steroid-producing cells comes from the plasma, but there is also de novo synthesis of cholesterol in steroid-producing cells. Because the steroids are highly lipid soluble, once they are synthesized, they simply diffuse across the cell membrane and enter the interstitial fluid and then the blood.

(Ref. Guyton & Hall-11th edition; Page 906)

3. ***Amine hormones** are derived from tyrosine* : The two groups of hormones derived from tyrosine, the thyroid and the adrenal medullary hormones, are formed by the actions of enzymes in the cytoplasmic compartments of the glandular cells. The thyroid hormones are synthesized and stored in the thyroid gland and incorporated into macromolecules of the protein *thyroglobulin*, which is stored in large follicles within the thyroid gland. Hormone secretion occurs when the amines are split from thyroglobulin and the free hormones are then released into the blood stream. After entering the blood, most of the thyroid hormone combines with plasma proteins, especially *thyroxine-binding globulin*, which slowly releases the hormones to the target tissues.

Epinephrine and *norepinephrine* are formed in the adrenal medulla, which normally secretes about four times more epinephrine than norepinephrine. Catecholamines are taken up into preformed vesicles and stored until secreted. Similar to the protein hormones stored in secretory granules, catecholamines are also released from adrenal medullary cells by *exocytosis*. Once the catecholamines enter the circulation, they can exist in the plasma in free form or in conjugation with other substances.

(Ref. Guyton & Hall-11th edition; Page 908)

Hormone Secretion

Onset of hormone secretion after a stimulus, and durations of action of different hormones :

i. Some hormones, such as *norepinephrine* and *epinephrine*, are secreted within seconds after the gland is stimulated. and they may develop full action within another few seconds to minutes.

ii. The actions of other hormones, such as thyroxine or growth hormone, may require months for full effect. Thus, each of the different hormones has its own characteristic onset and duration of action- each tailored to perform its specific control function.

(Ref. Guyton &Hall-11th edition; Page 908)

Feedback control of hormone secretion

1. *Negative feedback prevents overactivity of hormone systems:* Although the plasma concentrations of many hormones fluctuate in response to various stimuli that occur throughout the day, all hormones studied thus far appear to be closely controlled. In most instances, this control is exerted through negative feedback mechanisms that ensure a proper level of activity of the hormone at the target tissue. After a stimulus causes release of the hormone, conditions or products resulting from the action of the hormone tend to suppress its further release. In other words, the hormone (or one of its products) has a negative feedback effect to prevent oversecretion of the hormone or overactivity at the target tissue.

   The controlled variable is often not the secretory rate of the hormone itself but the degree of activity of the target tissue. Therefore, only when the target tissue activity rises to an appropriate level will feedback signals to the endocrine gland become powerful enough to slow further secretion of the hormone. Feedback regulation of hormones can occur at all levels, including gene transcription and translation steps involved in synthesis of the hormone and steps involved in processing the hormone or releasing the stored hormone.

2. *Surges of hormones can occur with positive feedback* : In a few instances, positive feedback occurs when the biological

action of the hormone causes additional secretion of the hormone. One example of this is the *surge of luteinizing hormone (LH)* that occurs as a result of the stimulatory effect of estrogen on the anterior pituitary before ovulation. The secreted LH then acts on the ovaries to stimulate additional secretion of estrogen, which in turn causes more secretion of LH. Eventually, LH reaches an appropriate concentration, and typical negative feedback control of honnone secretion is then exerted.

3. *Cyclical variations occur in hormone release* : Superimposed on the negative and positive feedback control of hormone secretion are periodic variations in hormone release that are influenced by seasonal changes, various stages of development and aging, the diurnal (daily) cycle, or sleep. For example, the secretion of *growth hormone* is markedly increased during the early period of sleep but is reduced during the later stages of sleep. In many cases, these cyclical variations in hormone secretion are due to changes in activity of neural pathways involved in controlling hormone release.

(Ref. Guyton & Hall-11th edition; Page 909)

Transport of hormones in the blood

1. *Water-soluble hormones* (peptides and catecholamines) are dissolved in the plasma and transported from their sites of synthesis to target tissues, where they diffuse out of the capillaries, into the interstitial fluid, and ultimately to target cells.

2. *Steroid and thyroid hormones*, in contrast, circulate in the blood mainly bound to plasma proteins. Usually less than 10 per cent of steroid or thyroid hormones in the plasma exist free in solution. For example, more than 99 per cent of the thyroxine in the blood is bound to plasma proteins. However, protein-bound hormones cannot easily diffuse across the capillaries and gain access to their target cells and are therefore biologically inactive until they dissociate from plasma proteins.

   The relatively large amounts of hormones bound to proteins serve as reservoirs, replenishing the concentration of free hormones when they are bound to target receptors or lost from the circulation. Also, binding of hormones to plasma proteins greatly slows their clearance from the plasma.

(Ref. Guyton & Hall-11th edition; Page 909)

Clearance of hormones from the blood

Two factors can increase or decrease the concentration of a hormone in the blood.

1. Rate of hormone secretion into the blood.
2. Rate of removal of the hormone from the blood, which is called the metabolic clearance rate. This is usually expressed in terms of the number of milliliters of plasma cleared of the hormone per minute. To calculate this clearance rate, one measures- *i.* the rate of disappearance of the hormone from the plasma per minute and *ii.* the concentration of the hormone in each milliliter of plasma. Then, the metabolic clearance rate is calculated by the *following formula* :

   Metabolic clearance rate = Rate of disappearance of hormone from the plasma / Concentration of hormone in each milliliter of plasma.

Hormones are 'cleared' from the plasma in several ways, including :

i. Metabolic destruction by the tissues
ii. Binding with the tissues
iii. Excretion by the liver into the bile
iv. Excretion by the kidneys into the urine.

Hormones are sometimes degraded at their target cells by enzymatic processes that cause endocytosis of the cell membrane hormone-receptor complex; the hormone is then metabolized in the cell, and the receptors are usually recycled back to the cell membrane.

i. Most of the *peptide hormones* and *catecholamines* are water soluble and circulate freely in the blood. They are usually degraded by enzymes in the blood and tissues and rapidly excreted by the kidneys and liver, thus remaining in the blood for only a short time. For example, the half-life of angiotensin II circulating in the blood is less than a minute.
ii. Hormones that are *bound to plasma proteins* are cleared from the blood at much slower rates and may remain in the circulation for several hours or even days. The half-life of adrenal steroids in the circulation, for example, ranges between 20 and 100 minutes, whereas the half-life of the protein-bound thyroid hormones may be as long as 1 to 6 days.

(Ref. Guyton & Hall-11th edition; Page 909)

Mechenisms of action of hormones

Receptors for hormones, neurotransmitters & other ligands

The first step of a hormone's action is to bind to *specific receptors* at the target cell. Cells that lack receptors for the hormones do not respond. When the hormone combines with its receptor, this usually initiates a cascade of reactions in the cell, with each stage becoming more powerfully activated so that even small concentrations of the hormone can have a large effect.

Hormonal receptors are large proteins, and each cell that is to be stimulated usually has some 2000 to 100,000 receptors. Also, each receptor is usually highly specific for a single hormone; this determines the type of hormone that will act on a particular tissue. The target tissues that are affected by a hormone are those that contain its specific receptors.

Location of receptors : The locations for the different types of hormone receptors are generally the following :

1. *In or on the surface of the cell membrane* : The membrane receptors are specific mostly for the *protein, peptide*, and *catecholamine* hormones.
2. *In the cell cytoplasm* : The receptors for the different *steroid hormones* are found almost entirely in th cytoplasm.
3. *In the cell nucleus* : The receptors for the *thyroxine* hormones are found in the nucleus and are believed be located in direct association with one or more of the chromosomes.

Regulation of the number of hormone receptors : The number of receptors in a target cell usually does not remain constant from day to day, or even from minute to minute.

i. ***Down-regulation*** : When a hormone or neurotransmitter is present in excess, the number of active receptors generally decreases called down-regulation.

Causes :

a. In the case of receptors in the membrane, receptor-mediated endocytosis is responsible for down-regulation in some instances; ligands bind to their receptors, and the ligand-receptor complexes move laterally in the membrane to coated pits, where they are taken into the cell by endocytosis *(internalization)*. Internalization of β_2-adrenergic receptors triggers an increase in receptor mRNA degradation so that the number of receptors is decreased.

b. Some receptors are recycled after internalization, where as others are replaced by *de novo synthesis* in the cell.

c. Another type of down-regulation is *desensitization*, in which receptors are chemically modified in ways that make them less responsive.

ii. ***Up-regulation*** : Where as in the presence of a deficiency of the chemical messenger, there is an increase in the number of active receptors called up-regulation.

Exception : Angiotensin II in its actions on the adrenal cortex is an exception; it increases rather than decreases the number of its receptors in the adrenal.

(Ref. Ganong 22th edition; page-37)

Desensitisation

Prolonged exposure to their ligands causes most receptors to become unresponsive, ie. to undergo desensitisation.

Types :

i. *Homologous desensitisation* : Loss of responsiveness only to the particular ligand and maintained responsiveness of the cell to other ligands.

ii. *Heterologous desensitisation* : In which the cell becomes unresponsive to other ligands as well.

(Ref. Ganong 22th edition; page 97)

Structure of receptor :

1. Ligand binding site :

Function :

a. Recognise the ligand

b. Affinity to specific ligand.

2. Active site :

Function : For post binding events. Also determines whether the ligand is agonist or antagonist and acts accordingly.

Affinity : Specific receptor has affinity to specific ligand.

Target tissue : The selective cell or tissue on which a particular hormone act is called target tissue.

Ligand : A ligand is a substance which can combine with the receptor. A ligand, thus may be a hormone or a drug molecule.

Intracellular signaling after hormone receptor activation

Almost without exception, a hormone affects its target tissues by first forming a hormone-receptor complex. This alters the function of the receptor itself, and the activated receptor initiates the hormonal effects. To explain this, let us give a few examples.

1. *Some hormones change membrane permeability* : Virtually all the neurotransmitter substances, such. as *acetylcholine* and *norepinephrine*, combine with receptor in the postsynaptic membrane. Almost always this causes a change in the structure of the receptor, usually opening or closing a channel for one or more ions. Some receptors open (or close) *channels for sodium ions*, others for *potassium ions*, others for *calcium ions*, and so forth. It is the altered movement of these ions through the channels that causes the subsequent effects on the postsynaptic cells. A few of the circulating hormones, such as *epinephrine* and *norepinephrine* secreted by the adrenal medulla, have similar effects to open or close membrane ion channels.
2. *Some hormones activate intracellular enzymes when they combine with their receptors* : Another common effect of hormone binding to membrane receptors is activation (or occasionally inactivation) of an enzyme immediately inside the cell membrane. A good example of this is the effect of *insulin*. Insulin binds with that portion of its membrane receptor that protrudes to the exterior of the cell. This produces a structural change in the receptor molecule itself, causing the portion of the molecule that protrudes to the inside to become an *activated kinase*. This kinase then promotes phosphorylation several different substances inside the cell. Most of the actions of insulin on the cell result secondarily from these phosphorylation processes.

A second example, one widely used in hormonal control of cell function, is for the hormone to bind with a special transmembrane receptor that then becomes the activated enzyme *adenylyl cyclase* at the end that protrudes to the interior of the cell. This cyclase in turn catalyzes the formation of cAMP, and cAMP has a multitude of effects

inside the cell to control cell activity, as discussed in greater detail later, cAMP is called a *second messenger* because it is not the hormone itself that directly institutes the intracellular changes; instead, it is the cAMP that serves as a second messenger to cause these effects.

For a few peptide hormones, such as *atrial natriuretic peptide* (ANP), *cyclic guanosine monophosphate* (cGMP), which is only slightly different from cAMP, serves in a similar manner as a second messenger.

3. *Some hormones activate genes by binding with intracellular receptors* : Several hormones, especially the *steroid hormones* and *thyroid hormones*, bind with protein receptors inside the cell, not in the cell membrane. The activated hormone-receptor complex then binds with or activates specific portions of the DNA strands of the cell nucleus, which in turn initiates transcription of specific genes to form messenger RNA (mRNA). Therefore, minutes, hours, or even days after the hormone has entered the cell, newly formed proteins appear in the cell and become the controllers of new or increased cellular functions.

(Ref. Guyton & Hall-11th edition; Page 910, 911)

Second messenger mechanisms for mediating intracellular hormonal functions

We noted earlier that one of the means by which hormones exert intracellular actions is to stimulate formation of the second messenger cAMP inside the cell membrane. The cAMP in turn causes subsequent intracellular effects of the hormone. Thus, the only direct effect that the hormone has on the cell is to activate a single type of membrane receptor. The second messenger does the rest.

cAMP is not the only second messenger used by the different hormones. Two other especially important- i. calcium ions and associated calmodulin and ii. products of membrane phospholipid breakdown.

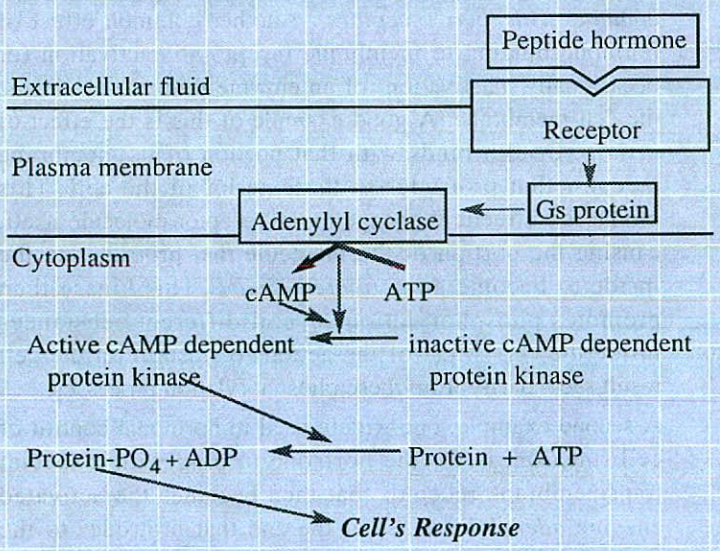


Fig 8-3. *Cyclic adenosine monophosphate (cAMP) mechenism by which many hormones exert their control of cell function.*

1. ***The adenylyl cyclase-cAMP second messenger system*** Binding of the hormones with the receptor allows coupling of the receptor to a *G-protein*. If the G-protein stimulates the adenylyl cyclase-cAMP system, it is called a G_S-protein, denoting a stimulatory G-protein. Stimulation of adenylyl cyclase, a membrane-bound enzyme, by the G_S-protein then catalyzes the conversion of a small amount of cytoplasmic *adenosine triphosphate* (ATP) into cAMP inside the cell. This then activates *cAMP dependent protein kinase*, which phosphorylates specific proteins in the cell, triggering biochemical reactions that ultimately lead to the cell's response to the hormone.

   Once cAMP is formed inside the cell, it usually activates a cascade of enzymes. That is, a first enzyme is activated, which then activates another enzyme, which activates a third, and so forth. The importance of this mechanism is that only a few molecules of activated adenylyl cyclase immediately inside the cell membrane can cause many more molecules of the next enzyme to be activated, which can cause still more molecules of the third enzyme to be activated, and so forth. In this way, even the slightest amount of hormone acting on the cell surface can initiate a powerful cascading activating force for the entire cell.

   If binding of the hormone to its receptors is coupled to an inhibitory G-protein (denoted G_i-protein), adenylyl cyclase will be inhibited, reducing the formation of cAMP and ultimately leading to an inhibitory action in the cell. Thus, depending on the coupling of the hormone receptor to an inhibitory or a stimulatory G-protein, a hormone can either increase or decrease the concentration of cAMP and phosphorylation of key proteins inside the cell.

   The specific action that occurs in response to increases or decreases of cAMP in each type of target cell depends on the nature of the intracellular machinery- some cells having one set of enzymes, and other cells having other enzymes. Therefore, different functions are elicited in different target cells- such functions as initiating synthesis of specific intracellular chemicals, causing muscle contraction or relaxation, initiating secretion by the cells, and altering cell permeability.

   Thus, a thyroid cell stimulated by cAMP forms the metabolic hormones thyroxine and triiodothyronine, whereas the same cAMP in an adrenocortical cell causes secretion of the adrenocortical steroid hormones. However, cAMP affects epithelial cells of the renal tubules by increasing their permeability to water.

   Hormones that use the adenylyl cyclase-cAMP second messenger system :

   1. Adrenocorticotropic hormone (ACTH)
   2. Angiotensin II (epithelial cell)

3. Calcitonin
4. Catecholamines (β receptors)
5. Follicle-stimulating hormone (FSH)
6. Glucagon
7. Human chorionic gonadotropin (HCG)
8. Luteinizing hormone (LH)
9. Parathyroid hormone (PTH)
10. Secretin
11. Thyroid-stimulating hormone (TSH)
12. Vasopressin (V_2 receptor, epithelial cell).

(Ref. Guyton & Hall-11th edition; Page 913)

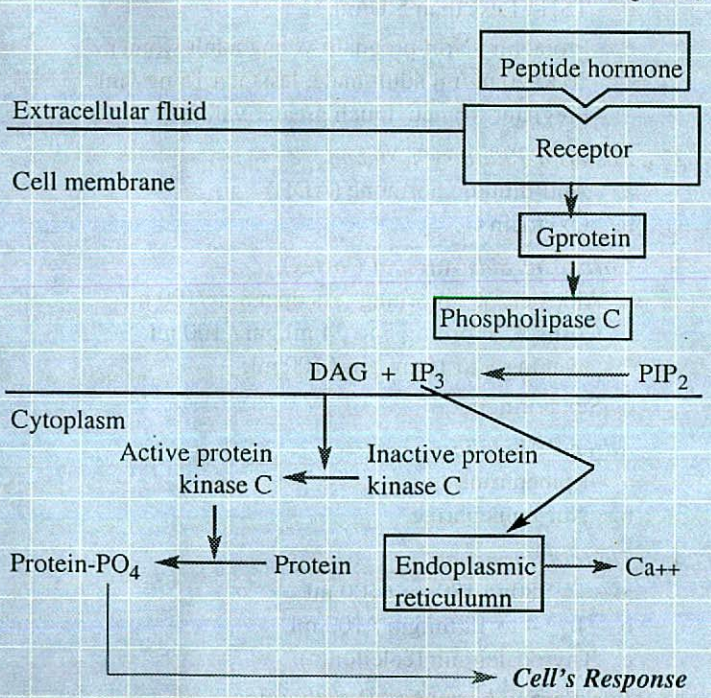


Fig 8-4. *Cell membrane phospholipids second messenger system by which some hormone exert their control of cell function. DAG, diacylglycerol; IP_3, inositol triphosphate; PIP_2, phosphatidylinositol biphosphate.*

2. ***The cell membrane phospholipids second messenger system*** : Some hormones activate transmembrane receptors that activate the enzyme *phospholipase C* attached to the inside projections of the receptors. This enzyme catalyzes the breakdown of some phospholipids in the cell membrane, especially *phosphatidylinositol biphosphate (PIP_2)*, into two different second messenger products, *inositol triphosphate (IP_3)* and *diacylglycerol (DAG)*. The IP_3 mobilizes calcium ions from mitochondna and the endoplasmic reticulum, and the calcium ions then have their own second messenger effects, such as smooth muscle contraction and changes in cell secretion.

   DAG, the other lipid second messenger, activates the enzyme *protein kinase C (PKC)*, which then phosphorylates a large number of proteins, leading to the cell's response. In addition to these effects, the lipid portion of DAG is *arachidonic acid*, which is the precursor for the prostaglandins and other local hormones that cause multiple effects in tissues throughout the body.

   Hormones use the phospholipase C second messenger system :

   1. Angiotensin II (vascular smooth muscle)
   2. Catecholamines (α receptor)
   3. Gonadotropin-releasing hormone (GnRH)
   4. Growth hormone-releasing hormone (GHRH)
   5. Oxytocin
   7. Thyroid-releasing hormone
   8. Vassopressin (V_1 receptor, vascular smooth muscle).

   (Ref. Guyton & Hall-11th edition; Page 914)

3. ***The calcium-calmodulin second messenger system*** : This operates in response to the entry of calcium into the cells. The calcium entry may be initiated- i. by changes in membrane potential that open membrane calcium channels or ii. by a hormone interacting with membrane receptors that open calcium channels.

   On entering a cell, calcium ions bind with the protein *calmodulin*. This protein has four calcium sites, and when three or four of these sites have bound with calcium, the calmodulin changes its shape and initiates multiple effects inside the cell, including activation or inhibition of protein kinases. Activation of calmodulin dependent protein kinases causes, via phosphorylation, activation or inhibition of proteins involved in the cell's response to the hormone. For example, one specific function of calmodulin is to activate myosin kinase, which acts directly on the myosin of smooth muscle to cause smooth muscle contraction.

   The normal calcium ion concentration in most cells of the body is 10^{-8} to 10^{-7} mol/L, which is not enough to activate the calmodulin system. But when the calcium ion concentration rises to 10^{-6} to 10^{-5} mol/L, enough binding occurs to cause all the intracellular actions of calmodulin. This is almost exactly the same amount of calcium ion change that is required in skeletal muscle to activate *troponin C*, which in turn causes skeletal muscle contraction. It is interesting that troponin C is similar to calmodulin both in function and in protein structure.

   (Ref. Guyton & Hall-11th edition; Page 914)

Hormones that act mainly on the genetic machinery of the cell

1. ***Steroid hormones increase protein synthesis*** : Another means by which hormones act - specifically the steroid hormones secreted by the *adrenal cortex, ovaries*, and *testes* - is to cause synthesis of proteins in the target cells; these proteins then function as enzymes, transport proteins, or

structural proteins that in turn provide other functions of the cells.

The sequence of events in steroid function is essentially the following :

1. The steroid hormone enters the cytoplasm of the cell, where it binds with a specific *receptor protein.*
2. The combined *receptor protein-hormone* then diffuses into or is transported into the nucleus.
3. The combination binds at specific points on the DNA strands in the chromosomes, which activates the transcription process of specific genes to form messenger RNA.
4. The messenger RNA diffuses into the cytoplasm, where it promotes the translation process at the ribosomes to form new proteins.

Example : ***Aldosterone***, one of the hormones secreted by the adrenal cortex, enters the cytoplasm of renal tubular cells, which contain a specific aldosterone receptor protein. Therefore, in these cells, the sequence of events cited earlier ensues. After about 45 minutes, proteins begin to appear in the renal tubular cells and promote sodium reabsorption from the tubules and potassium secretion into the tubules. Thus, there is a characteristic delay in the initial action of the steroid hormone of at least 45 minutes and up to several hours or even days for full action. This is in marked contrast to the almost instantaneous action of some of the peptide and amino acid-derived hormones, such as *vasopressin* and *norepinephrine*.

2. ***Thyroid hormones increase gene transcription in the cell nucleus*** : The thyroid hormones thyroxine and triiodothyronine cause increased transcription by specific genes in the nucleus. To accomplish this, these hormones first bind directly with receptor proteins in the nucleus itself; these receptors are probably protein molecules located within the chromosomal complex, and they probably control the function of the genetic promoters or operators.

   Two important features of thyroid hormone function in the nucleus are the following :

   i. They activate the genetic mechanisms for the formation of many types of intracellular proteins- probably 100 or more. Many of these are enzymes that promote enhanced intracellular metabolic activity in virtually all cells of the body.

   ii. Once bound to the intranuclear receptors, the thyroid hormones can continue to express their control functions for days or even weeks.

(Ref. Guyton & Hall-11th edition; Page 915)

Approximate normal values (by RIA method) of concentrations of some important hormones in plasma/serum.

1. Adenohypophysial hormones (Anterior Pituitary):
   a. ACTH : 10 to 80 pg /ml.
   b. Gonadotrop(h)ins :
      i. Women, reproducing age -
      FSH : 8 to 12 IU / liter; during FSH surge value may reach near 20 IU / liter.
      LH : about 15 IU/liter; during LH surge value may reach about 80 IU/liter.
      ii. Women, post menopausal age - values are shigher.
   c. Growth Hormone : Less than 5 ng / ml, after 100 gm of oral glucose.
   d. TSH : Less than 5 U/ml.
   e. Prolactin : Non-pregnant young adult women. 10 to 20 ng/ml adult male, lessthen 15 ng / ml. Pregnant women, much greater values.
2. *Posterior Pituitary hormone*
   a. Anti-diuretic hormone (ADH)
   b. Oxytocin.
3. *Corticosteroids(Adrenal Cortex)*
   a. Aldosterone : morning less than 8 ng/100 ml.
   b. Cortisol : morning 5 to 24 mi.gm / 100 ml, evening 3 to 10 mi.gm / 100 ml.
   c. Sex hormone

   Adrenal Medulla:
   a. Epinephrine
   b. Nor-epinephrine
4. *Thyroid hormones*
   a. T_3 : 80 to 180 ng / 100 ml.
   b. T_4 : 4 to 12 mi.gm / 100 ml.
   c. Thyrocalcitonin(calcitonin)

   Parathyriod hormone: Parathormone.
4. *Sex Steroids (Ovary)*
   a. In women reproducing age, *Estradiol :* 20 to 60 pg /ml; higher values in ovulation peak.
   Progesterone : pre ovulatory, <2 ng / ml, post ovulatory > 4.5 ng / ml.
   b. *Adult males (Testes)*
   Testosterone : 250 to 1000 ng / 100 ml.
5. *Pancreatic hormones*
   a. Glucagon : 50 to 100 pg / ml.
   b. Insulin : Fasting 5 to 25 m U/ml; value rises sharply after meals.
6. *Hyphothalamic Hormones (Hypothalamus)*
   a. Thyrotropin releasing hormone (TRH) : Which causes release of thyroid-stimulating hormone.
   b. Corticotropin releasing hormone (CRH) : Which causes release of adrenocorticotropin.
   c. Growth hormone releasing hormone (GHRH) : Which casues relase of growth hormone and growth hormone

inhibitory hormone (GHIH)- which is the same as the hormone somatostatin and which inhibits the release of growth hormone.

d. Gonadotropin releasing hormone (GnRH) : Which causes release of the two gonadotropic hormones, luteinizing hormone and follicle stimulating hormone.

e. Prolactin inhibitory hormone (PIH) : Which causes inhibition of prolactin secretion.

Radioimmunoassay

Antibodies to the polypeptides and proteins are readily produced, and, by using special techniques, it is possible to make antibodies to the other chemical messengers as well. The antibodies can be used to measure the messengers in body fluids and in tissue extracts by *radioimmunoassay*.

This technique depends on the fact that the naturally occurring, unlabeled ligand and added radioactive ligand compete to bind to an antibody to the ligand. The greater the amount of unlabeled ligand in the specimen being analysed, the more it competes and the smaller the amount of radioactive ligand that binds to the antibody.

Use : Radioimmunoassays are extensively used in research and in clinical medicine.

(Ref. Ganong 22th edition; page 37)

Difference between hormones & enzymes

Hormones	*Enzymes*
1. Hormone are generally both protein & steroid in nature.	1. Enzymes are always protein in nature.
2. They are secreted by definite endocrine glands or cell or group of cells.	2. Enzymes are always secretedby any tissue or cell.
3. Hormones act upon target tissue. It may be locally or distally.	3. Enzyme generally acts locally.
4. Hormones generally act by producing 3-5 cyclic AMP or specific protein which may be a enzyme.	4. Enzymes are organic catalysts and they act upon biochemical reactions.
5. Hormones are named according to the nature, source of origin & function.	5. Enzymes are named according to the chemical change they have done.
6. For hormone action definite receptor is required.	6. For enzymes action no such receptor is required
7. They generally regulate morphogenesis, development of gonads, secondary sex character etc.	7. They cannot regulate morphogenesis.
8. Hormones generally stimulate or inhibit hormone secretion by feed-back mechanism.	8. Enzyme cannot do so.

Functions of Hormones *(An overview)*

i. *Homeostasis* :
   a. Metabolism : e.g Insulin, Glucagon, Thyroid, Cortisol.
   b. Antistress action : eg Cortisol , ACTH, ADH Vaopressin, Adrenalin, Thyroid.
   c. Via water and mineral regulation : e.g ADH, Aldosterone, PTH.

ii. *Growth* : e.g Growth hormone, Somatomedin, IGF, Thyroid hormones, Testosterone.

iii. *Reproduction* : *e.g* Testicular/ovarian steroids, Gn RH Gonadotropins, Prolactin.

iv. *Combating emergency* : e.g Adrenalin and Noradrenalin.

Estimation of Hormones & hormonal status

1. Radioimmunoassay (RIA)
2. ELISA (enzyme linked immunosorvent assay) technic.
3. Flurimetric analysis
4. Cytochemical assay
5. Dynamic test.

First Massenger : These are the chemicals which directly acts on the receptor. These are-

1. Hormones
2. Neuro-transmitter.
3. Drugs.

Second massenger : These are the chemicals which are formed after the action of first massenger on the receptors. These are -

1. cAMP
2. Ca^{++} ion
3. IP_3.

Hypothalamus

The hypothalamic releasing hormones : Hypothalamus liberates hormones (or factors) which enter the adenohypophysis via the portal system of blood supply and strongly influences the secretions of the adenohypophysis.

1. *Thyrotropin releasing hormone (TRH) :* This is a tripeptide hormone. It acts on thyrotroph cells to cause secretion of TSH. TRH also acts on lactotroph and has some PRLRF like activities.

   Besides hypothalamus , TRH is also found in many other areas of the brain, spinal cord and even in the gastrointestinal tract.

2. *Corticotropin releasing hormone (CRH) :* It is a 41 amino acid peptide chain, secreted by the hypothalamus. The

posterior pituitary hormone ADH acts synergistically with the CRH on the corticotrophs to produce more ACTH. (CRH is produced by other areas of brain as well, most notably by the limbic system and cerebral cortex).

3. *Gonadotropin releasing hormone (GnRH)* : It is a decapeptide hormone. GnRH causes stimulation of secretion of both FSH and LH.
4. *Growth hormone releasing hormone GHRH (Somatocrinin)* : GHRH is a 44 amino acid peptide chain and it stimulates growth hormone secretion. Another GHRH with 40 amino acids is also known. The two GHRHs are known as GHRH 44 and GHRH 40 respectively.
5. *Somatostatin* : This contains 14 amino acids in the chain. In addition to the hypothalamus,the somatostatin is also secreted by the pancreatic islet cells and even gastric mucosa. Hypothalamic somatostatin depresses growth hormones secretion. Apart from its action on the somatotrophs of adenohypophysis, the somatostatin has many other functions.
6. Prolactin inhibitory factor (PIF).
7. Prolactin releasing factor : Its details are not known.

(Ref. Guyton & Hall-11th ed and Concise Medical Physiology)

Anterior Pituitary Gland

Physiological anatomy of pituitary gland : The pituitary gland, also called the hypophysis, is a small gland - about 1 cm in diameter and 0.5 to 1 gm in weight that lies in the sella turcica at the base of the brain and is connected with the hypothalamus by the pituitary (or hypophysial) stalk.

The pituitary gland is divided into two parts. Anterior pituitary or adenohypophysis and posterior pituitary or neurohypophysis, between them a relatively avascular zone, called pars intermedia which is almost absent in human being. Anterior pituitary develops from *Rathke's pouch* which is an embryonic invagination of pharyngeal epithelium and posterior pituitary develops from an outgrowth of the hypothalamus.

(Ref. Guyton & Hall-10th edition; Page 918)

Hormone secreting cells of the human anterior pituitary gland

Cell Type	*Hormones Secreted*	*% of Total secretory cells*	*Stain Affinity*	*Diameter of secretoty Granules (nm)*
Somatotrope	Growth hormone	50	Acidophilic	300-400
Lactotrope	Prolactin	10-30	Acidophilic	200
Corticotrope	ACTH, β-LPH	10	Basophilic	400-550
Thyrotrope	TSH	5	Basophilic	120-200
Gonadotrope	FSH, LH	20	Basophilic	250-400

(Ref. Ganong 22th edition, Page 397)

Q. ***Name the hormones of the anterior pituitary gland and their major functins.***

Ans. Please go throuh the page 8.2 for pituitary hormone. Then-

Intermediate lobe :

1. α-, β-, and γ-melanocyte-stimulating hormones (α-, β-, and γ-MSH; referred to collectively as melanotropin or intermedin).
   Function : Stimulate melanin synthesis in humans.
2. γ-Lipotropin (γ-LPH), corticotropin-like intermediate lobe peptide (CLIP), other fragments of pro-opiomelanocortin.
   Function : ?

N.B. In addition, a variety of gastrointestinal and other polypeptides are found in one or more lobes of the pituitary gland. These include CCK, gastrin, renin, angiotensin II, and calcitonin gene-related peptide (CGRP).

(Ref. Ganong 22th edition, Page 396)

Hypothalamo-hypophysial portal system

Hypothalamo-hypophysial portal system is a vascular connection which connects the hypothalamus with anterior pituitary.

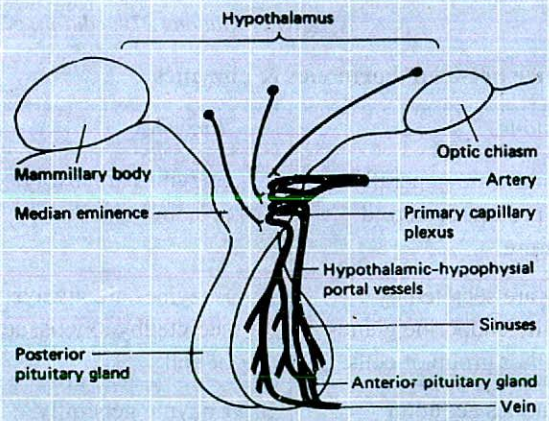


Fig. 8-5. *The hypothalamo hypophysial portal system.*

The anterior pitiutary is a highly vascular gland with extensive capillary sinuses among the glandular cells. Almost all the blood that enters these sinuses passes first through another capillary bed in the lower hypothalamus. The blood then flows through small *hypothalamic-hypophysial portal vessels* into the anterior pituitary sinuses. Figure 8-3. shows the lowermost portion of the hypothalamus called the *median eminence* that connects inferiorly with the pituitary stalk. Small arteries penetrate into the substance of the median eminence and then additional small vessels return to its surface, coalescing to form the hypothalamic-hypophysial portal vessels. These in turn pass downward along the pituitary stalk to supply blood to the anterior pituitary sinuses.

(Ref. Guyton & Hall-11th edition; Page 920)

Control of pituitary secretion by the hypothalamus

Almost all the secretion of pituitary gland are controlled by either hormonal or nervous signals from the hypothalamus. Secretion from posterior pituitary is controlled by the nerve signals originate in the hypothalamus and terminate in the posterior pituitary.

In contrast, secretion by the anterior pituitary is controlled by the *hypothalamic releasing* or *hypothalamic inhibitory hormones (or factors)* secreted within the hypothalamus itself and then conducted to the anterior pituitary through minute blood vessels called *hypothalamic-hypophysial portal vessels.* In the anterior pituitary, these releasing and inhibitory hormones act on the glandular cells to control their secretion.

The hypothalamous in turn receives signals from many sources in the nervous system. Thus, when a person is exposed to pain, a portion of the pain signal is transmitted into the hypothalamus. Likewise, when a person experiences some powerful depressing or exciting thought, a portion of the signal is transmitted into the hypothalamus. Olfactory stimuli denoting pleasant or unpleasant smells transmit strong signal components directly and through the amygdaloid nuclei into the hypothalamus. Even the concentration of the nutrients, electrolytes, water and various hormones in the blood excite or inhibit variuos portions of the hpothalamous. Thus the hypothalamous is a collecting center for information concerning the internal well being of the body, and in turn, much of this information is used to control secretions of the many globally important pituitary hormones.

(Ref. Guyton & Hall-11th edition; Page 919)

Growth Hormone (GH)

Chemistry of GH : Growth hormone is a small protein molecule containing 191 amino acid in a single chain. Its molecular wt. is 22,005.

((Ref. Guyton & Hall-11th edition; Page 922)

Blood level of growth hormone :

1. Adult : 1.6 to 3 ng/ml
2. Child : 6 ng/ml.

It may increase to as high as 50 ng/ml after depletion of the body stores proteins or carbohydrates during prolonged starvation.

(Ref. Guyton & Hall-11th edition; Page 924)

Daily secretion and half life of growth hormone : Growth hormone is metabolised rapidly, probably at least in part in the liver. The-half life of circulating growth hormone in humans is 6-20 minutes, and the daily growth hormone output has been calculated to be 0.2-1.0 mg/day in adults.

(Ref. Ganong 22th edition, Page 400)

Funtion of Growth hormone

1. ***Metabolic function :***
   a. *On protein metabolism : It increases protein deposition by :*
      i. Increasing amino acid transport through cell membrane.
      ii. Increasing protein synthesis by the ribosomes.
      iii. Increasing transcription of DNA to form RNA.
      iv. Decreasing catabolism of protein.
   b. *On fat metabolism : It increases fat utilization by -*
      i. Stimulating Beta oxidation of fatty acid
      ii. Increasing mobilization of fat from adipose tissue.
      iii. Increasing utilization of acetyl CoA.
      iv. It has ketogenic effect .
   c. *On carbohydrate metabolism :*
      i. Decreases peripheral utilization of glucose.
      ii. Increases gluconeogenesis.
      iii. Stimulate glycogenesis.
      iv. Decreases glycolysis.
2. ***Skeletal growth :*** Increase the growth of skeletal frame by-
   i. Increased deposition of protein by the chondrocytic and osteogenic cells that cause bone growth.
   ii. Increased rate of reproduction of these cells as well.
   iii. The specific effect of converting chondrocyte into osteogenic cells thus causing deposition of new bone.
3. ***General body growth :*** It stimulates the growth of all tissues of body which are capable of growing .
4. ***Miscellaneous function :*** Growth hormone increases the retention of some salt and electrolytes such as Na, K, Mg, Ca, PH_4, SO_4 etc.

(Ref. Guyton & Hall-11th edition; Page 922, 923)

Regulation of Growth hormone secretion

Secretion of growth hormones regulated by-

1. The precise mechenisms that control secretion of growth hormone are not fully understood, but several factors related to the person's state of nutrition or stress are known to stimulate secretion :
   i. Starvation, specially with severe *protein deficiency.*
   ii. Hypoglycemia or low concentration of fatty acids in the blood
   iii. Exercise
   iv. Excitement
   v. Trauma.

   And it characteristically increases during the first 2 hours of deep sleep.
2. *Hypothalamus :* Growth hormone secretion is controlled almost entirely in response to two factors secreted in the hypothalamus and then transported to the anterior pituitary gland through the hypothalamic-hypophysial portal vessels. These are growth hormone releasing hormone (GHRH).

and Growth hormone inhibitory hormone (GHIH), also called somatostatin.

3. Catecholamines, dopamine and serotonin, will also increase the rate of growth hormone secretion.

(Ref. Guyton & Hall-11th edition; Page 924)

Stimuli that affect growth hormone secretion in humans

A. ***Stimuli that increase growth hormone secretion*** :

1. Deficiency of energy substrate
   - Hypoglycemia
   - 2-Deoxyglucose
   - Exercise
   - Fasting
2. Increase in circulating levels of certain amino acids
   - Protein meal
   - Infusion of arginine and some other amino acids
3. Glucagon
4. Stressful stimuli
   - Pyrogen
   - Lysine vasopressin
   - Various psychologic stresses
5. Going to sleep
6. L-Dopa and α-adrenergic agonists that penetrate the brain
7. Apomorphine and other dopamine receptor agonists
   Estrogens and androgens.

B. ***Stimuli that decrease growth hormone secretion*** :

1. REM sleep
2. Glucose
3. Cortisol
4. FFA
5. Medroxyprogesterone
6. Growth hormone.

(Ref. Ganong 22th edition, Page 405)

Ketogenic effect of growth hormone : Under the influence of excessive amounts of growth hormone, fat mobilization from adipose tissue sometimes becomes so great that large quantities of acetoacetic acid are formed by the liver and released into the body fluids, thus causing *ketosis*. This excessive mobilization of fat from the aidipose tissue also frequently causes a fatty liver.

(Ref. Guyton & Hall-11th edition; Page 923)

Growth hormone decreases carbohydrate utilization *(Diabetogenic effects of growth hormone)* : Growth hormone causes multiple effects that influence carbohydrate metabolism, including- i. decreased glucose uptake in tissues such as skeletal muscle and fat, ii. increased glucose production by the liver, and iii. increased insulin secretion. Each of these changes results from growth hormone-induced *insulin resistance*, which attenuates insulin's actions to stimulate uptake and utilization of glucose in skeletal muscle and fat and to inhibit glucose output by the liver; this leads to increased blood glucose concentration and a compensatory increase in insulin secretion. For these reasons, growth hormone's effects are called ***diabetogenic***, and excess secretion of growth hormone can produce metabolic disturbances very similar to those found in patients with type II diabetes (non-insulin-dependent diabetes), who are also very resistant to the metabolic effects of insulin.

(Ref. Guyton & Hall-11th edition; Page 923)

Q. Why growth hormone is called protein and carbohydrate sparer?

Ans. Growth hormone has a specific effect in causing release of fatty acids from adipose tissue and, therefore, increasing the concentration of fatty acids in the body fluids. In addition, in tissues throughout the body, it enhances the conversion of fatty acids to acetyl coenzyme A (acetyl CoA) and subsequent utilization of this for energy. Therefore, under the influence of growth hormone, *fat is used for energy in preference to use of both carbohydrates and proteins.*

Growth hormone's effect to promote fat utilization, together with its protein anabolic effect, causes an increase in lean body mass. However, growth hormone mobilization of fat requires several hours to occur, whereas enhancement of protein synthesis can begin in minutes under the influence of growth hormone.

(Ref. Guyton & Hall-11th edition; Page 922, 923)

Growth factors

Growth factors have become increasingly important in many different aspects of physiology. They are polypepides and proteins that are conveniently divided into three groups.

i. *One group* is made up of agents that foster the multiplication or development of various types of cells :
   a. Nerve growth factor
   b. Insulin-like growth factor I IGF-I)
   c. Activins
   d. Inhibins
   e. Epidermal growth factor (EGF) etc.
   (More than 20 have been described)

ii. *Second group* : The cytokines are a second group. These factors are produced by macrophages and lymphocytes and are important in regulation of the immune system.
   Example : IL-1, IL-3, IL-4, IL-5, IL-6, IL-11etc.
   (More than 20 have been described)

iii. *Third group* : is made up of the colony-stimulating factors that regulate proliferation and maturation of red and white blood cells.
   Example : Stem cell factor (SCF), granulocyte colony stimulating factor (G-CSF), macrophage colony stimulating factor M-CSF), GM-CSF etc.

(Ref. Ganong 22th edition; page- 44; 520)

Growth periods

There are two periods of rapid growth, the first in *infancy* and the second in *late puberty* just before growth stops. The first period of accelerated growth is partly a continuation of the fetal growth period. The second growth spurt, at the time of puberty, is due to growth hormone, androgens, and estrogens, and the subsequent cessation of growth is due in large part to closure of the epiphyses by estrogens. Since girls mature earlier than boys, this growth spurt appears earlier in girls. Of course, in both sexes the rate of growth of individual tisstics varies.

It is interesting that at least during infancy, growth is not a continuous process but is episodic or saltatory. Increases in length of human infants of 0.5-2.5 cm in a few days are separated by periods of 2-63 days during which no measurable growth can be detected. The cause of the episodic growth is unknown.

(Ref. Ganong 22th edition, Page-404)

Catch-up Growth

Following illness or starvation in children, there is a period of *catch-up-growth* during which the growth rate is greater than normal. The acelerated growth usually continues until the previous growth curve is reached, then slows to normal. The mechenism that bring about and control catch-up growth are unknown.

(Ref. Ganong 22th edition, Page 406)

Disorder of secretion of anterior pituitary

1. *Hyperactivity or Hyperpituitarism* :
   a. *Gigantism or giantism* : In the young before union of the epiphysis of the long bones.
   b. *Acromegaly* : After union of the epiphysis of the long bones.
   c. *Cushing syndrome* : (Pituitary basophilism).
   d. Other Hormone-Secreting Tumors : Prolactin-secreting tumors are common.
2. *Hypoactivity or Hypopituitarism :*
   a. *Dwarfism* : Pituitary insufficiency in the young produces Dwarfism.
   b. In the adult it causes - Simmond's cachexiar or sheehan's syndrome.
   c. Acromicria (Rare).

(Ref. (Ref. Ganong 21th edition; and Shahana 2nd-695)

Panhypopituitarisn

This term means decreased secretion of all the anterior pituitary hormones.

Cause : It may be

i. Congenital (present from birth). Or,
ii. Suddenly occur. Or,
iii. May occur slowly at any period of life.

Panhypopituitarism in adult (Shelhan's syndrom) :

Cause : It occurs in two tumoric conditions

i. Cranipharyngiomas
ii. Chromophobe tumor.

It may also occurs in thrombosis of the pituitary blood vessel.

Effect or features :

i. Hypothyroidism.
ii. Decrease production of glucocorticoids by the adre nal gland.
iii. Suppressed secretion of the gonadotropic hormones to the point that sexual functions are lost.

(Ref. Guyton & Hall-11th edition; Page 926)

Dwarfism

Most instances of dwarfism result from generalized deficiency of anterior pituitary secretion (panhypopituitarism) during childhood. In general, all the physical parts of the body develop in appropriate proportion to one another, but the rate of development is greatly decreased. A child who has reached the age of 10 years may have the bodily development of a child of 4 to 5 years, and the same person on reaching the age of 20 years may have the bodily development of a child of 7 to 10 years.

(Ref. Guyton & Hall-11th edition; Page 926)

Short stature can be due to- i. GRH deficiency, ii. growth hormone deficiency, iii. deficient secretion of IGF-I, or iv. other causes. Isolated growth hormone deficiency is often due to GRH deficiency, and in these instances, the growth hormone response to GRH is normal. However some patient with isolated growth hormone deficiency have abnormalities of their growth hormone-secreting cells.

1. ***Laron dwarfism*** : In this group of dwarfed children, the plasma growth hormone concentration is normal or elevated but their growth hormone receptors are unresponsive as a result of loss-of-function mutations of the gene for the receptors. The resulting condition is known as *growth hormone insensitivity* or *Laron dwarfism*. Plasma IGF-I is markedly reduced, along with IGFBP-3, which is also growth hormone-dependent.
2. *Psychosocial dwarfism* or the ***Kaspar Hauser syndrome*** : Chronic abuse and neglect can also cause dwarfism in children. This condition is known as psychosocial dwarfism or the Kaspar Hauser syndrome, named for the patient with the first reported case.
3. ***Achondroplasia***, the most common form of dwarfism in humans, is characterized by short limbs with a normal trunk. It is an autosomal dominant condition caused by a mutation in the gene that codes for *fibrohlast growth factor receptor 3 (FGFR3)*. This member of the fibroblast growth receptor family is normally expressed in cartilage and the brain.

(Ref. Ganong 22th edition, Page 407)

Gigantism

Patho-physiology (cause) : Occasionally, the acidophilic, growth hormone-producing cells of the anterior pituitary gland become excessively active, and sometimes even acidophilic tumors occur in the gland. As a result, large quantities of growth hormone are produced. All body tissues grow rapidly, including the bones. If the condition occurs before adolescence, before the epiphyses of the long bones have become fused with the shafts, height increases so that the person becomes a giant as tall as 8 feet.

Effects :

1. The giant ordinarily has *hyperglycemia*.
2. The *beta cells of the islets of Langerhans* in the pancreas are *prone to degenerate* because they become overactive owing to the hyperglycemia. Consequently, in about 10 per cent of giants, *full-blown diabetes mellitus* finally develops.
3. In most giants, *panhypopituitarism* eventually develops if they remain untreated, because the gigantism is usually caused by a tumor of the pituitary gland that grows until the gland itself is destroyed.

   This eventual general deficiency of pituitary hormones usually causes death in early adulthood.

Management : However, once gigantism is diagnosed, further effects can often be blocked by microsurgical removal of the tumor from the pituitary gland or by irradiation of the gland.

(Ref. Guyton & Hall-11th edition; Page 926)

Acromegaly

Tumors of the somatotropes of the anterior pituitary secrete large amounts of growth hormone, leading in adults to *acromegaly*. Hypersccretion of growth hormone is accompanied by hypersecretion of prolactin in 20-40% of patients with acromegaly. In addition, secretion of glycoprotein hormone α subunits is said to occur in up to 37% of patients. Acromegaly can be caused by extrapituitary as well as intrapituitary growth hormone-secreting tumors and by hypothalamic tumors that secrete GRH, but these are rare.

Clinical features :

1. The principal findings in acromegaly are those related to the local effects of the tumor
   a. Enlargement of the sella turcica
   b. Headache
   c. Visual disturbances.
2. Those due to growth hormone secretion.
   a. Enlargement of the hands and feet (***acral parts***; hence the term acromegaly) and a protrusion of the lower jaw (prognathism).
   b. Overgrowth of the malar, frontal, and facial bones combines with prognathism to produce the coarse facial features called *acromegalic facies*.
   c. Body hair is increased in amount.
   d. The skeletal changes predispose to osteoarthritis.

About 25% of patients have abnormal glucose tolerance tests, and 4% develop lactation in the absence of pregnancy.

(Ref. Ganong 21th edition, Page-413)

Posterior Pituitary

The posterior ptuitary gland, also called *neurohypophysis*, is composed mainly of glial-like cells called *pituicytes*. However, the pituicytes do not secret hormones; they act simply as a supporting structure for large numbers of *terminal nerve fibres* and *terminal nerve endings* from nerve tracts that originate in the *supraoptic* and *paraventri cular nuclei* of the hypothalamus. These tract pass to the neurohypo physis through the pituitary stalk *(hypophy sial stalk)*.

(Ref. Guyton & Hall-11th edition; Page 927)

Hormones of the posterior pituitary :

i. Anti-diuretic homone (ADH), also called vasopressin.

ii. Oxytocin.

(Ref. Guyton & Hall-11th edition; Page 927)

Site of ADH & oxytocin secretion : ADH is fromed primarily in the the supraoptic nuclei, whereas oxytocin is fromed primarily in the the paraventricular nuclei of the hypothalamus. Each of these nuclei can synthesize about one sixth as much of the second hormone as of its primary hormone.

(Ref. Guyton & Hall-11th edition; Page 928)

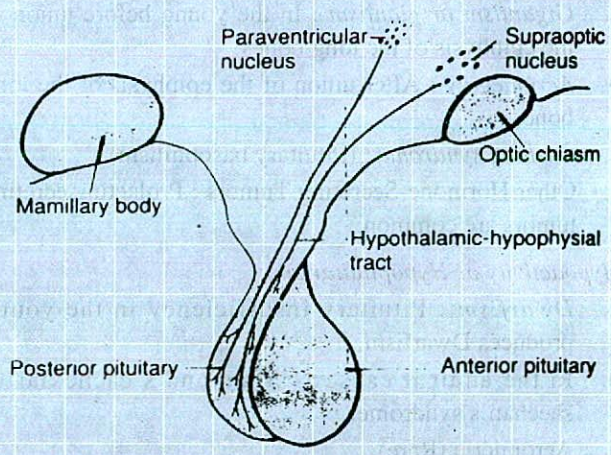


Fig. 8-6. *Hypothalamic control of the posterior pituitary.*

Function of ADH

A. *Antidiuretic effect :*

1. It causes reabsorption of water from kidney tubule (collecting ducts and tubules).
2. It maintains osmolarity and Na^+ concentration in extracellular fluid.
3. It reduces Cl^- absorption and increases Cl^- loss.

B. *Vasoconstrictor and pressure effects* : Higher concentration

of ADH have a potent effect of constricting the arterioles throughout the body and therefore of increasing the arterial pressure. For this reason, ADH has another name, *vasopressin*.

(Ref. Guyton & Hall-11th edition; Page 928)

Function of Oxytocin

1. *On pregnant uterus :* Toward the end of gestation it causes contraction of fundus and body and relaxation of cervix of uterus, hence helps in parturation.
2. *On non-pregnant uterus :* It increases the receptive contraction of non pregnant uterus during coitus and helps in transport of spermatoza.
3. *On milk ejection by the breast :* It causes constriction of myoepithelial cells of lactating mammary gland to expell the accumulated milk from the alveoli of the ducts after suckling stimuli on the nipple.

(Ref. Guyton & Hall-11th edition; Page 929)

Mechanism of water reabsorption by ADH

or Physiologic functions of ADH : Extremely minute quantities of ADH -as small as 2 nanograms when injected into a person can cause decreased excretion of water by the kidneys (antidiuresis).

Briefly, in the absence of ADH, the collecting tubules and ducts become almost impermeable to water, which prevents significant reabsorption of water and therefore allows extreme loss of water into the urine, also causing extreme dilution of the urine. Conversely, in the presence of ADH, the permeability of the collecting ducts and tubules to water increases greatly and allows most of the water to be reabsorbed as the tubular fluid passes through these ducts, thereby conserving water in the body and producing very concentrated urine.

Mechenism : The mechanism by which ADH acts on the ducts to increase their permeability is only partially known. Without ADH, the luminal membranes of the tubular epithelial cells are almost impermeable to water. However, immediately inside the cell membrane are a large number of special vesicles that have highly water-permeable pores called aquaporins. When ADH acts on the cell, it first combines with membrane receptors that cause the formation of cAMP inside the tubular cell cytoplasm. This in turn causes phosphorylation of elements in the special vesicles, which then causes the vesicles to insert into the apical cell membranes, thus providing many areas of high water permeability.

Duration : All this occurs within 5 to 10 minutes. Then in the absence of ADH, the entire process reverses in another 5 to 10 minutes.

Effects : Thus, this process temporarily provides many new pores that allow free diffusion of water from the tubular fluid to the peritubular fluid. Water is then absorbed from the collecting tubules and ducts by osmosis.

(Ref. Guyton & Hall-11th edition; Page 928)

Regulation of ADH production

1. *Osmotic regulation* : When a concentrated electrolyte solution is injected into the artery that supplies the hyothalamus, the ADH neurons in the supraoptic and paraventricular nuclei immediately transmit impulses into the posterior pituitary to release large quantities of ADH into the circulating blood, sometimes increasing the ADH secretion to as high as 20 times normal. Conversely, injection of a dilute solution into this artery causes cessation of the impulses and therefore almost total cessation of ADH secretion. Thus, the concentraon of ADH in the body fluids can change from small amounts to large amounts, or vice versa, in only a few minutes.

   The precise way that the osmotic concentration of the extracellular fluids controls ADH secretion is not clear. Yet somewhere in or near the hypothalamus are modified neuron receptors called *osrnoreceptors*.

   a. *When the extracellular fluid becomes too concentrated*, fluid is pulled by osmosis out of the osmoreceptor cell, dccreasg its size and initiating appropriate nerve signals in the hypothalamus to cause additional ADH secretion.

   b. Conversely, *when the extracellular fluid becomes too dilute*, water moves by osmosis in the opposite direction, into the cell, and this decreases the signal for ADH secretion.

   Although some research workers place these osmoreceptors in the hypothalamus itself (possibly even in the supraoptic nuclei themselves), others believe that they are located in the *organum vasculosum*, a highly vascular structure in the anteroventral wall of the third ventricle.

2. Regardless of the mechanism, concentrated body fluids do stimulate the supraoptic nuclei, whereas dilute body fluids inhibit them. Therefore, a feedback control system is available to control the total osmotic pressure of the body fluids.

(Ref. Guyton & Hall-11th edition; Page 928, 929)

Inappropriate hypersecretion of antidiuretic hormone (SIADH) : In this syndrome vasopressin (ADH) is responsible not only for dilutional hyponatremia but also for loss of salt in the urine when water retention is sufficient to expand the ECF volume, reducing aldesterone secretion. This occurs in patients with cerebral disease *(cerebral salt wasting)* and pulmonary disease *(pulmonary salt wasting)*.

Hypersecretion of vasopressin in patients with pulmonary diseases such as lung cancer may be due in part to the interruption of inhibitory impulses in vagal afferents from the stretch receptors in the atria and great veins. However, a significant number of lung tumors and some other cancers secrete vasopressin.

Patients with inappropriate hypersecretion of vassopressin have

been succesfully treated with demeclocycline, an antibiotic that reduces the renal response to vasopressin.

(Ref. Ganong 22th edition; page-246)

Oxytocin

Oxytocin causes contraction of the pregnant uterus : The hormone oxytocin, in accordance with its name, powerfully stimulates contraction of the pregnant uterus, especially toward the end of gestation. Therefore, many obstetricians believe that this hormone is at least partially responsible for causing birth of the baby. This is supported by the following facts :

i. In a hypophysectomized animal, the duration of labor is prolonged, thus indicating a possible effect of oxytocin during delivery.

ii. The amount of oxytocin in the plasma increases during labor, especially during the last stage.

iii. Stimulation of the cervix in a pregnant animal elicits nervous signals that pass to the hypothalamus and cause increased secretion of oxytocin.

(Ref. Guyton & Hall-11th edition; Page 929)

Oxytocin aids in milk ejection by the breasts : Oxytocin also plays an especially important role in *lactation*. In lactation, it causes milk to be expressed from the alveoli into the ducts of the breast so that the baby can obtain it from the ducts by suckling.

Mechanism : The suckling stimuli on the nipple of the breast cause signals to be transmitted through sensory nerves to the oxytocin neurons in the paraventricular and supraoptic nuclei in the hypothalamus, which causes release of oxytocin by the posterior pituitary gland. The oxytocin then is carried by the blood to the breasts, where it causes contraction of *myo-epithelial cells* that lie outside of and form a latticework surrounding the alveoli of the mammary glands. In less than a minute after the beginning of suckling, milk begins to flow. This mechanism is called *milk letdown* or *milk ejection.*

(Ref. Guyton & Hall-11th edition; Page 929)

Regulation of secretion of oxytocin

Stimulation of the paraventricular nucleus causes its neuronal cells to secrete the hormone oxytocin. This in turn causes increased contractility of the uterus as well as contraction of the myoepithelial cells that surround the alveoli of the breasts, which then causes the alveoli to empty the milk through the nipples. At the end of pregnancy, especially large quantities of oxytocin are secreted, and this secretion helps to promote labor contractions that expel the baby. Also, when a baby suckles the mother's breast, a reflex signal from the nipple to the posterior hypothalamus causes oxytocin release and the oxytocin then performs the necessary function of contracting the ductules of the breast, thereby expelling milk through the nipples so that the baby can nourish itself. *(Ref. Guyton & Hall-11th edition; Page 929)*

Thyroid gland

Physiologic anatomy of thyroid gland : Thyroid gland consists of large numbers of follicles (100-300 meters in diameter) filled with a proteinous secretory substance called colloid. The follicle is lined by single layer of cuboidal epithelial cells which become flattened in inactive state and become tall columnar in active state.

Major constituent of colloid is thyroglobulin which contains the thyroid hormones within its molecules. It also contain mono-iodotyrosin, di-iodotyrosin, tri-iodotyrosin.

The thyroid gland has a blood flow about five times the weight of the gland each minute, which is a blood supply as rich as that of any other area of the body; with the possible exception of the adrenal cortex.

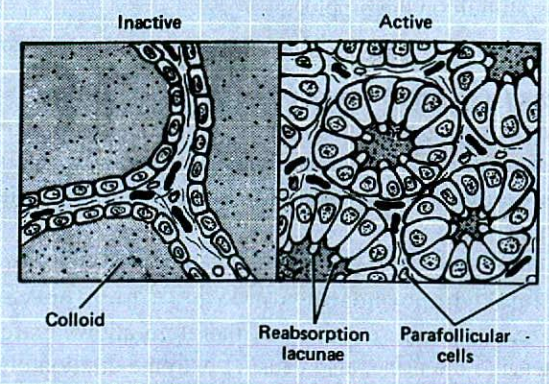


Fig. 8-7. *Thyriod histology.*

The thyroid gland begins to function from the midterm of fetal life. Food, iodine deficiency in the mother diet may lead to hypo function of the thyroid in the fetus and its consequent hazards.

i. *Weight :* 20 gm

ii. *Number of follicles :* 3 million.

iii. *Diameter of each follicle* : 100-300 μm

iv. *Types of cells :*

a. Follicular cells : These secrete *thyroxine (T_4) and Tri-iodothyronin (T_3).*

b. Para follicular cells : These secrete *thyrocalcitonin.*

About 93% of metabolically active hormones secreted by the thyroid gland is thyroxine and 7% is triiodothyronine. However, almost all the thyroxine is eventually converted to triidothyronine in the tissues.

(Ref. Guyton & Hall-11th edition; Page 931)

Functions of thyroid cells :

1. They collect and transport iodine.
2. They synthesize thyroglobulin and secret it into the colloid.
3. They remove the thyroid hormones from thyroglobulin and secret them into the circulation.

(Ref. Ganong 22th edition, Page 319)

Difference between inactive and active condition of thyroid follicle :

Active	*Inactive*
1. Cells become columner.	1. Cells become flat and squamous.
2. The lining epithelium increases and become folded.	2. Do not increases.
3. Mitochondria and golgi complex increases in the cell.	3. Mitochondria less in number.
4. Vesicles are irregular and basophilic in stain.	4. Regular and acidic in stain.

Thyroglobulin

This is a large glycoprotein molecules. This glycoprotein is made up of two subunits. T_3 and T_4 are synthesized in the colloid by iodination and condensation of tyrosine molecules bound in peptide linkage in thyroglobulin.

Molecular weight : 660,000.

Content :

i. Carbohydrate- 10% by weight.
ii. 123 tyrosine residues, but only 4-8 of these are normally incorporated into thyroid hormones.

Site of synthesis : Endoplasmic reticulumn and Golgi apparatus of thyroid cells synthesize and secrets into the colloids by exocytosis of granules that also contains thyroid peroxidase.

Serum level : 6 ng/ml *(Ref. Ganong 22th edition)*

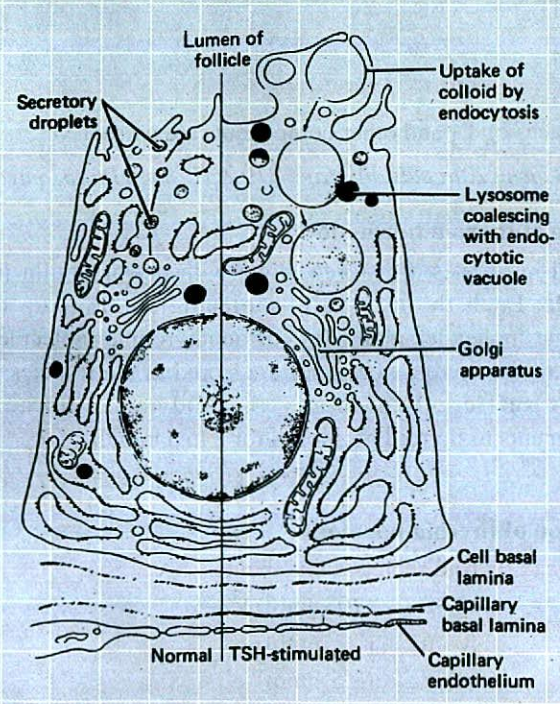


Fig. 8-8. *Thyroid cell.*

Thyroid hormones remain bound to thyroglobulin until secreted. When thyroid hormones are secreted , colloid is ingested by the thyroid cells, the peptide bonds are hydrolyzed, and free T_4 and T_3 are discharged into the capillaries.

(Ref. Ganong 22th edition, Page 319 & Guyton 11th ed; P 932)

Requirement of iodine for formation of thyroxine

To form normal quantities of thyroxin about 50 mg of iodine in the form of iodides are required each year and 1 mg/ week.

To prevent iodine deficiency, common table salt is iodized with about 1 part sodium iodide to every 100,000 parts sodium chloride.

(Ref. Guyton & Hall-11th edition; Page 931)

Sources of iodine :

1. Table salt : iodized salt
2. Sea fish, vegetables near sea land
3. Water etc.

Fate of ingested iodine : After absorption from the intestine into the blood most of them are rapidly excreted by the kidneys, but only after about one fifth are selectively removed from the circulating blood by the cells of the thyroid gland and for synthesis of the thyroid hormone.

(Ref. Guyton & Hall-11th edition; Page 931)

Iodine metabolism

Iodine is a raw material essential for thyroid hormone synthesis. Ingested iodine is converted to iodide and absorbed.

1. *Minimum daily iodine intake* : The minimum daily iodine intake that will maintain normal thyroid function is 150 µg in adults, but in the United States the average dietary intake is approximately 500 µg/d.
2. *Normal plasma I^- level* is about : 0.3 µg/dL.
3. *I^- distribution* :
   a. I^- is distributed in a 'space' of approximately 25 L (35% of body weight). The principal organs that take up the I^- are the thyroid, which uses it to make thyroid hormones, and the kidneys, which excrete it in the urine.
   b. About 120 µg/d enter the thyroid at normal rates of thyroid hormone synthesis and secretion. The thyroid secretes 80 µg/d as iodine in T_3 and T_4.
   c. 40 micrograms of I^- per day diffuses into the ECF.
   d. The secreted T_3 and T_4 are metabolized in the liver and other tissues, with the release of 60 mg of I^- per day into the ECF.

   The total amount of I^- entering the ECF is thus 500 + 40 + 60, or 600 µg/d; 20% of this I^- enters the thyroid, whereas 80% is excreted in the urine.
5. *Excretion* : Some thyroid hormone derivatives are excreted in the bile, and some of the iodine in them is reabsorbed (enterohepatic circulation), but there is a net loss of I^- in the stool of approximately 20 µg/d.

(Ref. Ganong 22th edition, Page-317)

Iodide trapping or *iodide pump*

The thyroid concentrates iodide by actively transporting it from the circulation to the colloid. The transport mechanism is frequently called the *iodide-trapping mechanism* or *iodide pump*. The pump is an example of secondary active transport : Na^+ and I^- are cotransported into the thyroid cell, and the Na^+ is pumped into the interstitium by Na^+-K^+ ATPase. The Na^+-I^- cotransporter has been cloned and has 12 transmembrane domains with its amino and carboxyl terminals inside the cell.

The thyroid cell is about 50 mV negative relative to the interstitial area and the colloid; ie, it has a resting membrane potential of -50 mV. Iodide is pumped into the cell at its base against this electrical gradient, then diffuses down the electrical gradient into the colloid. In the gland, iodide is rapidly oxidized and bound to tyrosine.

N.B. The salivary glands, the gastric mucosa, the placenta, the ciliary body of the eye, the choroid plexus, and the mammary glands also transport iodide against a concentration gradient, but their uptake is not affected by TSH. The mammary glands also bind the iodine; diiodotyrosine is formed in mammary tissue, but T_4 and T_3 are not. The physiologic significance of all these extrathyroidal iodide-concentrating mechanisms is obscure.

(Ref. Ganong 22th edition, Page-319)

Synthesis of thyroid hormone

1. *Formation and secretion of thyroglobulin by the thyroid cells* : Each molecule of thyroglobulin contains about 70 tyrosine amino acids, and they are the major substrates that combine with iodine to form the thyroid hormones. The thyroxine and triiodothyronine hormones formed from the tyrosine amino acids remain part of the thyroglobulin molecule during synthesis of the thyroid hormones and even afterward as stored hormones in the follicular colloid.
2. *Oxidation of iodide ion* : In the thyroid gland, iodide is oxidized to iodine and bound in a matter of seconds to the 3 position of tyrosine molecules attached to thyroglobulin. The enzyme responsible for the oxidation and binding of iodide is *thyroid peroxidase*, with hydrogen peroxide accepting the electrons.
3. *Iodination of tyrosin and formation of thyroid hormone-'organification' of thyroglobulin* : The binding of iodine with the thyroglobulin molecule is called *organification* of thyroglobulin. Tyrosine is first iodinised to monoiodotyrosine. Monoiodotyrosine (MIT) is next iodinated in the 5 position to form diiodotyrosine (DIT). Two DIT molecules then undergo an oxidative condensation to form T_4 with the elimination of the alanine side chain from the molecole that forms the outer ring.
4. *Coupling* : There are two theories of how this coupling reaction occurs :
   a. One holds that the coupling occurs with both DIT molecules attached to thyroglobulin (intramolecular coupling).
   b. The other holds that the DIT that forms the outer ring is first detached from thyroglobulin (intermolecular coupling).

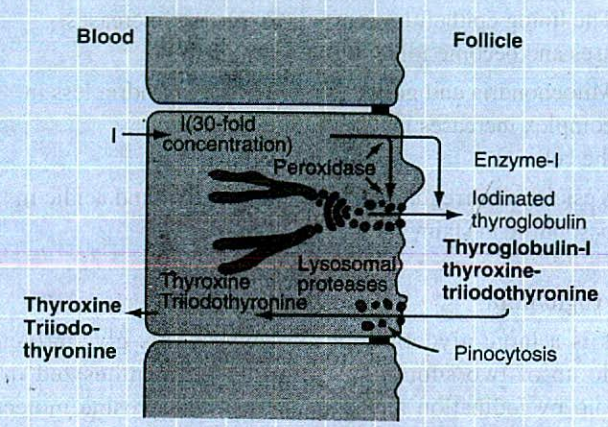


Fig. 8-9. *Thyroid cellular mechenisms for iodine transport, thyroxine and triiodothyronine formation, and thyroxine and triiodothyronine release into the blood.*

In any case, thyroid peroxidase is probably involved in coupling as well as iodination. T_3 is probably formed by condensation of MIT with DIT. A small amount of T_3 is also formed, probably by condensation of DIT with MIT.

In the normal human thyroid, the average distribution of iodinated compounds is :

MIT	: 23 %
DIT	: 33 %
T_4	: 35 %
T_3	: 07 %

Only traces of T_3 and other components are present.

(Ref. Ganong 22th edition, Page 319 & Guyton 11th ed; page 932)

Storage of thyroid hormone

Thyroid hormones are stored along with thyroglobulin in the colloids. Each thyroglobulin molecule contains up to 30 thyroxine molecules and a few triiodothyronine molecules. In this form, the thyroid hormones are stored in the follicles in an amount sufficient to supply the body with its normal requirements of thyroid hormones for 2 to 3 months.

(Ref. Guyton & Hall-11th edition; Page 933)

Secretion of thyroid hormone

The human thyroid secrets daily about-

1. T_4 : 80 µg (103 nmol)
2. T_3 : 04 µg (7 nmol)
3. RT_3 : 02 µg (3.5 nmol)

However, MIT and DIT are not secreted.

Procedure : The thyroid cells ingest colloid by endocytosis. This chewing away at the edge of the colloid produces the reabsorption lacunae seen in active glands. In the cells, the globules of colloid merge with lysosomes. The peptide bonds

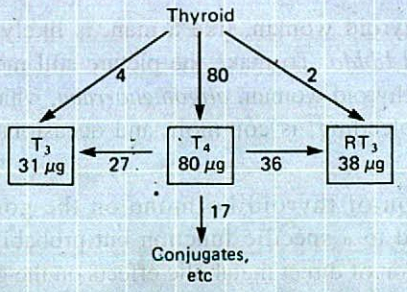


Fig. 8-10. *Secretion and interconversion of thyroid hormones in normal adult humans. Figures are in micrograms per day. Note that most of the T_3 and RT_3 are formed from T_4 deiodination in the tissues, and only small amounts are secreted by the thyroid.*

between the iodinated residues and the thyroglo bulin are broken by *proteases* in the lysosomes, and T_4, T_3, DIT, and MIT are liberated into the cytoplasm. The iodinated tyrosines are deiodinated by a microsomal *iodotyrosine deiodinase*. This enzyme does not attack iodinated thyronines, and T_4 and T_3 pass into the circulation. The iodine liberated by deiodination of MIT and DIT is reutilized in the gland and normally provides about twice as much iodide for hormone synthesis as the iodide pump does. In patients with congenital absence of the iodotyrosine deiodinase, MIT and DIT appear in the urine and there are symptoms of iodine deficiency.

(Ref. Ganong 21th edition, Page-322)

Transport of thyroid hormone

The normal total plasma level of thyroid hormone in adults is (approximately) :

1. T_4 : 8 μg/dL (103 nmol/L)
2. T_3 : 0.15 μg/dL (2.3 nmol/L).

Protein binding : Large amounts of both are bound to plasma proteins. Both are measured by radioimmunoassay.

The free thyroid hormones in plasma are in equilibrium with the protein-bound thyroid hormones in plasma and in tissues. Free thyroid hormones are added to the circulating pool by the thyroid. It is the free thyroid hormones in plasma that are physiologically active and that inhibit pituitary secretion of TSH.

Many other hormones are bound to plasma proteins, and there is an equilibrium between their free active forms and their bound inactive forms in the circulation. The function of protein-binding appears to be maintenance of a large pool of readily available free hormone. In addition, at least for T_3, hormone-binding prevents excess uptake by the first cells encountered and promotes uniform tissue distribution.

(Ref. Ganong 22th edition)

Binding of thyroid hormones to plasma proteins in normal adult humans :

Protein	*Plasma Concentration (mg/dL)*	*Amount of Circulating Hormone Bound*	
		T_4	T_3
Thyroxine binding globulin (TBG)	2	67	46
Thyroxine binding prealbumin (TBPA)	15	20	1
Albumin	3500	13	53

(Ref. Ganong 22 th edition; page-321)

Difference between T_3 & T_4

T_3	*T_4*
1. Its rapidity and intensity of action is 4 times potent than T_4.	1. It has less function than T_3
2. It has less affinity to bind with plasma protein.	2. It has high affinity to bind with plasma protein.
3. Its plasma concentration is less than T_4.	3. Its plasma concentration is more than T_3.
4. Duration of action is less.	4. Duration of action is more.
5. Contain one molecule of MIT & DIT.	5. It contains two molecule of DIT.

(Ref. Guyton & Hall-11th edition)

Mechanism of action of thyroid hormone : Most of the thyroxine secreted by the thyroid is converted to triiodothyronine. Intracellular thyroid hormone receptors have a very high affinity for triiodothyronine. Consequently about 90 per cent of the thyroid hormone molecules that bind with the receptors is triiodothyronine, and only 10 per cent thyroxine.

Thyroid hormones activate nuclear receptors : The thyroid hormone receptors are either attached to the DNA genetic strands or located in proximity to them. On binding with thyroid hormone, the receptors become activated and initiate the transcription process. Then large numbers of different types of messenger RNA are formed, followed within another few minutes or hours by RNA translation on the cytoplasmic ribosomes to form hundreds of new intracellular proteins. However not all the proteins are increased by similar percentages- some only slightly, and others at least as much as sixfold. It is believed that most, if not all, of the actions of thyroid hormone result from the subsequent enzymatic and other functions of these new proteins.

(Ref. Guyton & Hall 11th edition)

Functions of thyroid hormone

Some of the wide spread effects of thyroid hormones in the body are secondary to stimulation of O_2 consumption (*calorigenic action*), althogh the hormones also affect growth and development in mammals, help in regulation of lipid metabolism and increase the absorption of carbohydrates from the intestine. They also increase the dissociation of oxygen from hemoglobin by increasing red cell 2,3-diphosphoglycerate (DPG).

Physiologic effects of thyroid hormones :

Target tissue	*Effect*	*Mechanism*
Heart	Chronotropic	Increase number & affinity of β-adrenergic receptors.
	Inotropic	Enhance responses to circulating catecholamines. Increase proportion of alpha myosin heavy chain (with higher ATPase activity.
Adipose tissue	Catabolic	Stimulate lipolysis.
Muscle	Catabolic	Increase protein breakdown.
Bone	Developmental	Promote normal growth and skeletal development.
Nervous system	Developmental	Promote normal brain development.
Gut	Metabolic	Carbohydrate absorption
Lipo-protein	Metabolic	Stimulate formation of LDL receptors.
Other	Calorigenic	Stimulate oxygen consumption by metabobically active tissues (exceptions testes, uterus, lymph nodes, spleen, anterior pituitary) Increase metabolic rate.

(Ref. Ganong 22th edition; page 324)

Effects of thyroid hormones on growth : Thyroid hormones are essential for normal growth and skeletal maturation. In hypothyroid children, bone growth is slowed and epiphysial closure delayed. In the absences of thyroid hormones, growth hormone secretion is also depressed, and thyroid hormones potentiate of effect of growth hormone on the tissue.

(Ref. Ganong 22th edition, Page-326)

Effects of thyroid hormones on sextual function : For normal sexual function, thyroid secretion needs to be approximately normal. In men, lack of thyroid hormone is likely to cause *loss of libido*; great excesses of the hormone, however, sometimes cause *impotence*.

In women, lack of thyroid hormone often causes *menorrhagia* and *polymenorrhea*, that is, respectively, excessive and frequent menstrual bleeding. Yet, strongely enough, in other women thyroid lack may cause irregular periods and occasionally even *amenorrhea*.

A hypothyroid woman, like a man, is likely to have greatly *decreased libido*. To make the picture still more confusing, in the hyperthyroid woman, *oligomenorrhea*, which means greatly reduced bleeding, is common, and occasionally *amenorrhea* results.

The action of thyroid hormone on the gonads cannot be pinpointed to a specific function but probably results from a combination of direct metabolic effects on the gonads as well as excitatory and inhibitory feedback effects operating through the anterior pituitary hormones that control the sexual functions.

(Ref. Guyton & Hall-11th edition; Page 937)

Regulation of thyroid secretion

Thyroid function is regulated primarily by variations in the circulating level of pituitary TSH. TSH secretion is increased by

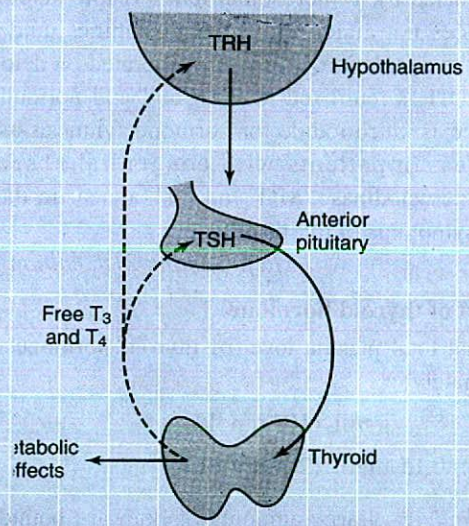


Fig. 8-11. *Feedback control of thyroid secretion. The dashed arrows indicate inhibitory effects, and the solid arrows indicate stimulatory effects*

the hypophysiotropic hormone *thyrotropin-releasing hormone (TRH)* and inhibited in a negative feedback fashion by circulating free T_4 and T_3. The effect of T_4 is enhanced by production of T_3 in the cytoplasm of the pituitary cells by the 5'-DII they contain. TSH secretion is also *inhibited by* stress, and in experimental animals it is *increased by* cold and *decreased by* warmth.

(Ref. Ganong 22th edition, Page-326)

Thyroid functions tests :

Thyroid functions tests are as follows-

1. *Determination of BMR* :
   In normal BMR : 40 cal/sq.m of surface

In hyperthyroidism : 50% above normal
In hypothyrodism : 30-40% below.

2. *Estimation of PBI (protein bind iodine) test* :
In normal : 4 to 8 µgm
In hyperthyroidism : More than 8 µgm
In hypothyroidism : Below than 4 µgm.

3. *Determination of Butanolextractable iodine test* :
In normal : 2-6 µgm/100 dl
In hyperthyroidism : Above 6 µgm %
In hypothyroidism : Below 2 µgm%.

4. *Determination of blood cholesterol level* :
In normal : 150 -300 mg%.
In hyperthyroidism : Become less than 150 mg %.
In hypothyroidism : Become more than 300 mg %.

5. *Determination of blood sugar level* :
Normally : 80-120 mg %
In hyperthyroidism : Above normal.
In hypothyroidism : Below normal.

6. *Determination of uptake of I^{131} by thyroid gland* :
Normal value : 0.75 µgm/day.
In hyperthyroidism : 40% above normal.
In hypothyroidism : 20% below normal.

7. *Thyroid suppression test* : Normally T_3 administration suppress the uptake of I^{131} by thyroid gland. In hyperthyroidism 20 times normal dose of T_3 cannot properly suppressed I^{131} uptake by the thyroid gland.

** *Direct test* :

1. *RIA (Radio-immunoassay)* : Normal serumvalue-
T_3 : 0.15 µg/dl (2.3 nmol/L)
T_4 : 8 µg/dl (103 nmol/L).
TSH: In hyperthyroidism, TSH concentration will be near zero whereas it is very high in hypothyroidism.
2. Thyroid imaging
3. Radio-active iodine uptake by thyroid cells.
4. FT_4.

Anti thyroid substances

Drugs that suppress the thyroid secretion are called antithyroid substances. The three best known of these are thiocyanate, propylthiouracil and high concentration of inorganic iodides.

The mechanism by which each of these blocks thyroid secretion are as follows -

i. *Thiocyanate* : By decreasing iodide tapping.
ii. *Propylthiouracil* : By depressing thyroid hormone formation.
iii. High concentration of *inorganic iodides*: By decreasing thyroid activity and thyroid gland size.

(Ref. Guyton & Hall-11th edition; Page 939).

Disorders of thyroid gland

The thyroid gland may undergo two types of disorders-

1. *Hperthyroidism* : When there is over secretion of thyroid hormones, the clinical syndroms is named as thyrotoxicosis. The most common cause is *Graves' disease (exophthalmic goitre)*.

Causes of hyperthyroidism :

i. *Thyroid overactivity*
   a. Graves' disease
   b. Solitary toxic adenoma
   c. Toxic multinodular goiter
   d. TSH-secreting pituitary tumor
   e. Thyroiditis
   f. Mutations causing constitutive activation of TSH receptors.

ii. *Extrathyroidal* :
   a. Administration of T3 or T4 (factitious or iatrogenic hyperthyroidism)
   b. Ectopic thyroid tissue.

2. *Hypothyroidism* : When there is under-secretion of thyroid hormones. This may affect children as well as adults.
   a. When it occurs in infants and children is called *cretinism.*
   b. When it affects adults is called *myxedema.*

Causes of congenital hypothyroidism :

a. Maternal iodine deficiency
b. Fetal thyroid dysgenesis
c. Inborn errors of thyroid hormone synthesis
d. Maternal antithyroid antibodies that cross the placenta
e. Fetal hypopituitary hypothyroidism.

(Ref. Ganong 22th edition, Page 328-329)

Hyperthyroidis (*thyrotoxicosis*)

Causes of thyrotoxicosis : The most common cause is *Graves' disease (exophthalmic goiter)*, although it may be caused by a variety of other disorders, including, in rare instances TSH-secreting tumors of the anterior pituitary or constitutive activation of the TSH receptor.

Four kinds of antibodies against the thyroid are found in thyroid disease. The mechenism responsible for the production of autoimmune antibodies against the thyroid is still unknown.

Hyperthyroidis (thyrotoxicosis) is characterized by / clinical F :

1. Nervousness
2. Weight loss
3. Hyperphagia
4. Heat intolerance
5. Increased pulse pressure
6. A fine tremor of the outstretched fingers
7. A warm soft skin

8. Sweating
9. BMR from +10 to as high as +100.

Thyrotoxicosis places a considerable load on the cardiovascular system, and particularly in elderly patients, most or even all the symptoms are cardiovascular. There is an increased incidence of atrial fibrillation, and the decrease in peripheral resistance as a result of cutaneous vasodilation predisposes patients to high output failure.

(Ref. Ganong 22th edition, Page 329)

Graves' disease (***exophthalmic goiter***)

Graves' disease is an autoimmune disease in which circulating antibodies formed against the TSH receptor activate the receptor, making the gland hyperactive. ***TSH receptor-stimulating antibodies*** *(TSH-R [stim] Ab)* are the antibodies responsible for Graves' disease.

In Graves' disease, there is marked stimulation of the secretion of thyroid hormones, and the high circulating T_4 and T_3 levels inhibit TSH secretion, so the circulating TSH level is depressed. Increasing levels of thyroid hormones tend to cause increased formation of the antibodies, whereas decreased levels produced by treatment of the disease tend to lower but not completely prevent formation of the antibodies.

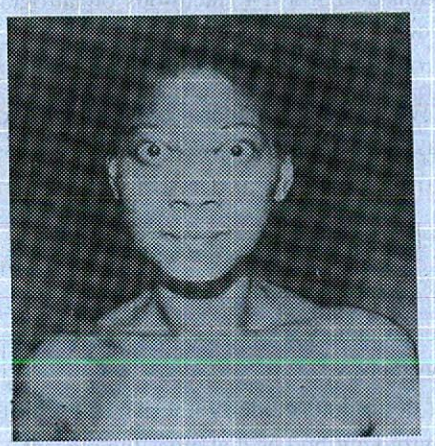


Fig. 8-12. *Graves' disease. Note the goiter and the exopthalmos.*

Clinica features : Same as thyrotoxicosis.

In Graves' disease, the thyroid is diffusely enlarged and there is often a protrusion of the eyeballs called *exophthalmos*.

(Ref. Ganong 22th edition, Page 329)

Hashimoto's thyroiditis : There are antibodies against thyroid peroxidase *(TPO Ab)* and TPO antibodies are elevated late in the course of chronic autoimmune thyroiditis (***Hashimoto's thyroiditis***), a condition in which thyroid cells are damaged and hypothyroidism may develop. In some cases of Hashimoto's thyroiditis, thyroid function is also inhibited by TSH-R [block] Ab.

(Ref. Ganong 22th edition)

Exophthalmos

Cause : The cause of of the exopthalmos is almost certainly an autoimmune attack on the extraocular muscles and orbital connective tissue by *cytotoxic antibodies*. The antibodies are formed to antigens common to the eye muscles and the thyroid. The condition responds to glucocorticoids or other agents that produce immunosuppression.

The exophthalmos in Graves' disease is due to swelling of the extraocular muscles and, to a lesser extent, the connective tissue within the rigid bony walls of the orbits. This pushes the eyeballs forward. Thyroid hormones are not directly responsible for the exophthalmos, and although exophthalmos is usually associated with hyperthyroidism and improves after treatment of the disease, it may occur before, during, or after the thyrotoxic state. In some patients with thyrotoxicosis, it is worse by thyroidectomy. In addition, it is occasionally seen in euthyroid patients with Hashimoto's thyroiditis, in patients with myxedema and in patients with no known thyroid disease.

(Ref. Ganong 22th edition, Page 329)

Iodine deficiency

When the dietary iodine intake falls below 50 µg/d, thyroid hormone synthesis is inadequate and secretion declines. As a result of increased TSH secretion, the thyroid hypertrophies, producing an ***iodine deficiency goiter*** that may become very large.

Such *endemic goiters* have been known since ancient times. Before the practice of adding iodide to table salt became widespread, they were very common in Central Europe and the area around the Great Lakes in the United States, the inland *goiter belts* where iodine has been leached out of the soil by rain so that food grown in the soil is iodine-deficient.

(Ref. Ganong 22th edition, Page 330)

Hypothyroidism

Hypothyroidism may be the end result of a number of diseases of the thyroid gland, or it may be secondary to pituitary failure (pituitary hypothyroidism) or hypothalamic failure (hypothalamic hypothyroidism). In the latter two conditions, unlike the first, the thyroid responds to a test dose of TSH, and at least in theory, hypothalamic hypothyroidism can be distinguished from the pituitary hypothyroidism by the presence in the former of a risc in plasma TSH following a test dose of TRH. The TSH response to TRH is usually normal in hypothalamic hypothyroidism, while it is increased in hypothyroidism caused by thyroid disease and decreased in hyperthyroidism because of the feedback of thyroid hormones on the pituitary gland.

(Ref. Ganong 22th edition, Page 328)

Myxedema

The syndrome of adult hypothyroidism is generally called *myxedema*, although this term is also used to refer specifically to the skin changes in this syndrome.

Clinical features :

1. In completely athyreotic humans, the BMR falls to about -40.
2. The hair is coarse and sparse

3. The skin is dry and yellowish (carotenemia)
4. Cold is poorly tolerated
5. The voice is husky and slow, the basis of the aphorism that '*myxedema is the one disease that can be diagnosed over the telephone.*'

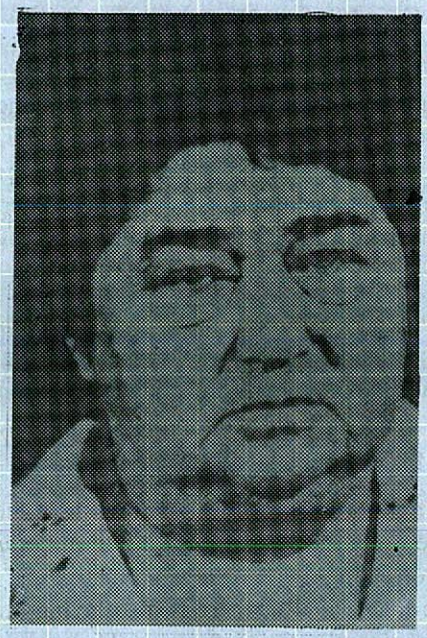


Fig. 8 -13. *A patient with myxedema.*

6. Mentation is slow
7. Memory is poor, and in some patients there are severe mental symptoms (*myxedema madness*).
8. Plasma cholesterol is elevated.

(Ref. Ganong 22th edition, Page 328)

Cretinism

Children who are hypothyroid from birth or before are called *cretins.*

Clinical features :

1. They are dwarfed and mentally retarded.
2. They have potbellies and enlarged, protruding tongues.

Worldwide, congenital hypothyroidism is one of the most common causes of preventable mental retardation.

Causes of cretinism or congenital hypothyroidism :

a. Maternal iodine deficiency
b. Fetal thyroid dysgenesis
c. Inborn errors of thyroid hormone synthesis
d. Maternal antithyroid antibodies that cross the placenta
e. Fetal hypopituitary hypothyroidism.

They include not only maternal iodine deficiency and various congenital abnormalities of the fetal hypothalamo-pituitary thyroid axis but also maternal antithyroid antibodies that cross the placenta and damage the fetal thyroid.

T_4 crosses the placenta, and unless the mother is hypothyroid, growth and development are normal until birth. If treatment is started at birth, the prognosis for normal growth and development is good. and mental retardation can generally be avoided; for this reason, screening tests for congenital hypothyroidism are routine in all states of the USA and most other developed countries.

When the mother is hypothyroid as well, as in the case of iodine deliciency, the mental deficiency is more severe and less responsive to treatment after birth. In addition, there may be deaf-mutism and rigidity. Increased use of iodized salt has now reduced the incidence of maternal iodine deficiency. However, it is still common in many parts of the world, and it has been estimated that 20 million people in the world now have various degrees of brain damage caused by iodine deficiency in utero.

(Ref. Ganong 22th edition, Page 328)

Goiter

Goiter means simply enlargement of thyroid gland. *Goiter is of two types* :

A. ***Endemic colloid goiter*** : This type of goiter occured specially in certain areas such as Swiss, Alps, in the Andes and in the great lakes region of US due to insufficient iodine present in the foodstuffs. So, this is called endemic colloid goiter.

Mehanism : Lack of iodine prevents the synthesis of thyroid hormone, as a result no hormone is available to inhibit the production of TSH by anterior pituitary, this allow the pituitary to secrete large quantities of TSH. This TSH causes the thyroid cells to secrete tremendous amount of *thyroglobulin colloid* in the follicle and the gland become larger and larger.

B. ***Idiopathic nontoxic colloid goiter :*** When enlargement of thyroid gland occurs in the person who do not have iodine deficiency. The exact cause of this goiter is unknown, but most patient show the signs of mild thyroioditis.

Therefore it is suggested that the thyroioditis causes slight hypothyroidism, which then increased TSH secretion and progressive enlargement of thyroid gland.

(Ref. Guyton & Hall-11th edition; Page 941)

Prevention of endemic goiter : Endemic goiter is prevented by :

1. Iodized salt : Common salt fortified with small quantities of sodium or potassium iodate. (1 in 100,000) .
2. Iodized oil : Intramuscular injection of iodized oil prevents endemic goitre.

Dose : 1-2 ml for adult.

(Ref : Community medicine Park.)

Calcitonin

This hormone is synthesized by the C cells (the parafollicular cells) of the thyroid. It is a peptide hormone containing 32

amino acids with a molecular weight of approximately 3400. As a result of the action of calcitonin, the serum calcium is lowered (thus acting in the opposite direction to that of PTH). Calcitonin prevents bone resorption. Calcitonin secretion is stimulated when the serum calcium level becomes high.

It is now established that calcitonin secretion is stimulated when there is secretion of the gastro intestinal hormones, gastrin & cholecystokinin pancreozymin, which are secreted after meals ; and it is in this period, calcium absorption from the gut rises. Teleologically, this may mean a mechanism aimed to see that the serum calcium does not become dangerously high and the extra calcium (in the serum, coming from food) is deposited on the bone. In addition glucagon also stimulates it.

The exact importance of calcitonin in man, however, is still unsettled.

Calcitonin is of proven help in the pagets disease (a rare disease,characterized by bony resorption and replacement by fibrous tissues and blood vesels).

Parathyroid Gland

Physiologic anatomy of parathyroid gland : Normally there are four parathyroid glands in the human being. These are located immediately behind the thyroid gland one behind each of the upper and each of the lower pole of the thyroid gland.

i. *Length :* 6 mm.
ii. *Wide :* 3 mm.
iii. *Thickness :* 2mm.
iv. *Parathyroid cells* :
   a. Chief cells : Secrets parathyroid (PTH).
   b. Oxyphil cells : Function is not certain but they are believed to be modified or depleted chief cells that no longer secrete hormone.

Removal of half of the parathyroid gland usually cause little physiological abnormality. Removal of 3of the 4 glands , cause *transient hypoparathyroidism*. But even a small quantity of parathyroid tissue is capable of hypertrophying satisfactorily to perform the function of all gland.

(Ref. Guyton & Hall-11th edition; page 978)

Bone

The adult compact bone contains about 75% inorganic material and 25% organic material (dry weight). Most of the inorganic material is calcium phosphate occurring mostly in a typical crystal form, called hydroxyapatite. The shape of the hydroxyapatite is such that it causes an increase in the surface area. Rest of the calcium phosphate is in amorphous form. The amorphous form is precursor of the crystalline form.

The calcium of the bone is in dynamic equilibrium with the calcium of the ECF, i.e, the calcium leaves the bone to enter the ECF and at the same time the ECF calcium is deposited in the bone, but there is no net gain or loss of calcium in either the bone or in the ECF, this dynamic equilibrium is seen in healthy adults. In the growing children Ca deposits in the bone. In osteoporesis, Ca is lost from the bone.

Bone, basically speaking, consists of a matrix of organic matter and the minerals. The matrix (also called the ground substance) consists of mucopolysaccharide and contains large number of collagen fibers.The matrix is heavily impregnated with minerals,chiefly the calcium salts, but other minerals like Mg also occur. Strontium, another element deserves special mention.

Strontium, which is a foreign metal, once introduced in the body,replaces calcium in the hydroxyapatite and remains there for many many years. Therefore radioactive strontium, once introduced in the body is difficult to remove, and it continues to emit harmful rays from the bone.

Throughout life, portions of bone, as a result of the action of parathormone, undergo resorption. The term ***resorption*** here means, lysis or eating away of organic matrix and removal of the inorganic material. But there is also laying down of new matrix and its mineralization (new bone deposition). These two processes, viz, resorption and new bone deposition, taken together constitute the process known as *remodelling.*

Bone cells : There are four tyes of bone cells
i. Osteoblasts
ii. Osteoclasts
iii. Osteocytes
iv. Osteoprogenitor or mesenchymal cells.

The osteoblasts have single nucleus and they deposit new bone. Osteoclasts are giant cells containing some 15 or 20 (sometimes as many as 100) nuclei. They cause resorption of bone. Functions of osteocyte, which are very small cells and are derived from osteoblasts, are not fully known.

Bone development : *The adult bone may develop in either of the two ways :*
i. Cartilaginous ossification.
ii. Membranous ossification.

In cartilaginous ossification, firstly, a cartilage is formed, subsequently,the cartilage is calcified, then the calcified cartilage undergoes resorption and in its place, bone is deposited.

In membranous ossfication, the initial cartilaginous phase does not appear. In general, the long bones like the femur and humerus develop in the cartilaginous way whereas the flat bones of skull are examples of membranous ossification. It should be remembered that calcified cartilage is not bone.

Parathormone

Is secreted by the chief cells of the parathyroid gland. It is protein in nature. It has a molecular weight 9,500 and is composed of 84 amino acids.

Chemistry of parathyroid hormon (Synthesis) : It is first synthesized on the *ribosomes* in the form of *prepro-parathormone*, a polypeptide chain of about 110 aminoacids. This is cleaved first to a prohormone 90 amino acids, then to the hormone itself with 84 amino acids by the *endoplasmic reticulumn* and *Golgi apparatus*, and finally is packaged in secretory granules in the cytoplasm of the cells.

Smaller compound with as few as *34 amino acids* adjacent to the N terminus of the molecule have also been isolated from the parathyroid glands that exhibit full PTH activity. In fact, because the kidneys rapidly removed the whole 84-amino acid hormone within minutes but fail to remove many of the *fragments* for hours, a large share of the hormonal activity is caused by the fragments.

(Ref. Guyton & Hall-11th edition; page 986)

Functions :

1. It increases the blood calcium level by -
   i. Resorption of Ca^{++} and PH_4^{+3} from bone.
   ii. Decreases excretion of calcium by the kidneys.
   iii. Absorption of Ca^{++} and PH_4^{+3} from intestine
2. It decreases the phosphate concentration by causing excessive renal phosphate excretion.

(Ref. Guyton & Hall-11th edition; page 985, 986)

Role of Parathormone on blood Ca^{++} level

Parathormone rises blood calcium level in three ways

A. *Resorption of Ca^{++} from bone* : It occurs in two phases-
   i. Slow phase
   ii. Rapid phase.

   In rapid phase, this hormone activate the calcium pump thereby causing rapid removal of calcium salt from bones i.e Ca^{++} mobilization from bone → this Ca^{++} reaches plasma → hypercalcaemia.

   In slow phase, this hormone activate the osteoclast cells. The activated osteoclasts then decrease deposition of calcium salt on bone and increase the blood Ca^{++} level.

B. *Decrease excretion of Ca^{++} from kidney* : Parathhormone binds with the receptors of the tubular epithelium which causes formation of cAMP, this increases the permeability of Ca^{++} through tubular epithelium and thus increases blood Ca^{++} level.

C. *Increase absorption of Ca^{++} from intestine* : Parathhormone increases the permeability of intestinal epithelium to calcium as that of kidney and thus increases the absorption of Ca^{++} from intestine.

(Ref. Guyton & Hall-11th edition; page 986)

Calcitonin

Role of calcitonin on blood Ca^{++} level : It decreases blood calcium level in three ways :

1. *Immediate effect* : It decreases the absorptive activities of the osteoclasts and passibly the osteolytic effect of osteocytic membrane throughout the bones and thus increases the Ca^{++} deposition in bony matrix.
2. *More prolonged effect* : It decreases the formation of new osteoclasts.
3. It reduce the osteoblastic activity.

NB. It prevents bone resorption.

(Ref. Guyton & Hall-11th edition; page 988)

Calcium metabloism

Distribution of Ca^{++} in plasma :

i. Normal plasma concentration of calcium : 9.4 mg/dl (about)
   : 2.4 mmol/L

(Ref. Guyton & Hall-11th edition; page 978)

ii. Normal plasma concentration of calcium : 10 mg/dl (about)
   : 2.5 mmol/L
   : 5 meq/L

(Ref. Ganong 22th edition, Page-382)

Distribution of calcium in normal human plasma :

1. *Nondiffusible (protein bound)* : Approximately 41% (1.0 mmol/L) of calcium combines with plasma protein which is nondiffusible through the capillary membrane.
2. *Diffusible combined with citrate and phosphate* : Approximately 9% (0.2 mmol/L) of the calcium is diffusible through the capillary membrane but is combined with ionic substances of plasma and inerstitial fluids (citrate and phosphate, for instance) in such a manner that it is not ionized.
3. *Diffusible and ionized* : The remaining 50% of the calcium in the plasma is both diffusible through the capillary membrane and ionized.

(Ref. Guyton & Hall-11th edition; page 978)

or

Distribution (mmol/L) of calcium in normal human plasma :

Total diffusible		1.34
Ionized (Ca^{++})	1.18	
Complexed to HCO3- , citrate etc.	0.16	
Total nondiffusible (protein-bound)		1.16
Bound to albumin	0.92	
Bound to globulin	0.24	
Total plasma calcium		2.50

It is the free, ionized calcium in the body fluids that is a vital

second messenger and is necessary for blood coagulation, muscle contraction, and nerve function.

(Ref. Ganong 22th edition, Page-383)

Total body calcium level : 1100 gm
: 27.5 mol

(Ref. Ganong 22th edition, Page-382)

Regulation of calcium metabolism

Three hormones are primarily concerned with the regulation of calcium metabolism.

1. *1,25-Dihydroxy-cholecalciferol* : Is a steroid hormone formed from vitamin D by successive hydroxylations in the liver and kidneys.
   Function : Its primary action is to increase calcium absorption from the intestine.
2. *Parathyroid hormone (PTH)* : Is secreted by the parathyroid glands.
   Function : Its main action is to mobilize calcium from bone and increase urinary phosphate excretion.
3. *Calcitonin* : A calcium-lowering hormone that in mammals is secreted primanly by cells in the thyroid gland,.
   Function : Inhibits bone resorption.

Although the role of calcitonin seems to be relatively minor, all three hormones probably operate in concert to maintain the constancy of the Ca^{2+} level in the body fluids.

A fourth hormone, *parathyroid hormone-related protein (PTHrP)*, acts on one of the PTH receptors and is important in skeletal development in utero. There may also be a phosphate-regulating hormone, and glucocorticoids, growth hormone, estrogens and various growth factors also affect calcium metabolism.

Other *electrolytes* and *pH* affect the Ca^{2+} level. Thus for example, *symptoms of tetany* appear at much higher total calcium levels if the patient ***hyperventilates,*** increasing plasma pH. Plasma proteins are more ionized when the pH is high, providing more protein anion to bind with Ca^{2+}.

(Ref. Ganong 22th edition, Page-382)

Calcium metabolism in an adult human

(ingesting 25 mmol; 1000 mg of calcium :

In bones : The calcium in bone is of two types : a *readily exchangeable reservoir* and a much larger pool of *stable calcium* that is only slowly exchangeable.

There are two *independent but interacting homeostatic systems* affecting the calcium in bone.

1. *One is the system* that regulates plasma Ca^{2+} and in the operation of this system, about 500 mmol of Ca^{2+} per day moves into and out of the readily exchangeable pool in the bone.
2. *The other system* is the one concerned with bone remodeling by the constant interplay of bone resorption and deposition, which, in the adult, accounts for 95% of bone formation. However, the Ca^{2+} interchange between plasma and this stable pool of bone calcium is only about 7.5 mmol/L.

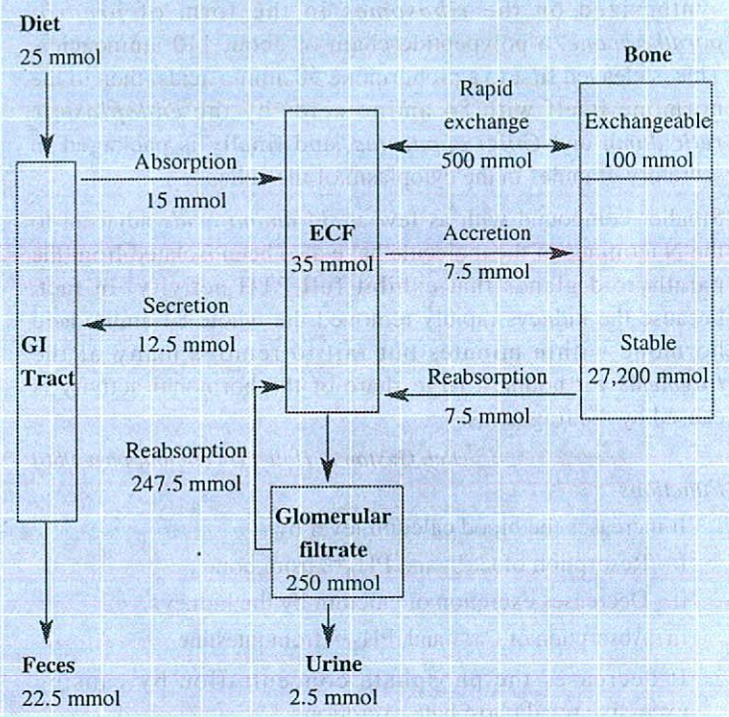


Figure 8-14. *Calcium metabolism in an adult human ingesting 25 mmol (1000 mg) of calcium per day.* (Ref. Ganong 22 th edition; page 386)

In kidneys : A large amount of calcium is filtered in the kidneys. but 98-99% of the filtered calcium is reabsorbed. About 60% of the reabsorption occurs in the *proximal tubules* and the remainder in the *ascending limb of the loop of Henle* and the *distal tubule*. Distal tubuIar reabsorption is regulated by parathyroid hormone.

In gastrointestinal tract : The absorption of Ca^{2+} from the gastrointestinal tract is actively transported out of the intestine by a system in the brush-border of the epithelial cells that involves a calcium-dependent ATPase, and this process is regulated by 1,25-dihydroxy cholecalciferol. There is also some absorption by passive diffusion. When Ca^{2+} intake is high, 1,25 dihydroxy cholecalciferol levels fall because of the increased plasma Ca^{2+}. Consequently, Ca^{2+} absorption undergoes adaptation; ie, it is high when the calcium intake is low and decreased when the calcium intake is high. Calcium absorption is also decreased by substances that form insoluble salts with Ca^{2+} (eg, phosphates and oxalates) or by alkalis, which favor formation of insoluble calcium soaps. A high-protein diet increases absorption in adults.

(Ref. Ganong 22th edition, Page-382, 383)

Hypocalcemic tetany : A decrease in extracellular Ca^{2+} exerts a net excitatory effect on nerve and muscle cells in vivo. The result is *hypocalcemic tetany*

Characteristics :

1. *Extensive spasms of skeletal muscle*, involving especially the muscles of the extremities and the larynx.
2. *Laryngospasm* becomes so severe that the airway is obstructed and fatal asphyxia is produced.

Ca^{2+}plays an important role in clotting in vivo, however, the level of plasma Ca^{2+} at which fatal tetany occurs is still above the level at which clotting defects would occur.

(Ref. Ganong 22th edition, Page 382)

Phosphorus

Phosphate is found in ATP, cAMP, 2,3-diphospho-glycerate, many proteins, and other vital compounds in the body. Phosphorylation and dephosphorylation of protein are involved in the regulation of cell function. Therefore, it is not surprising that phosphate metabolism is closely regulated.

Total body phosphorus : 500-800 gm
: 16.1-25.8 mol
85-90% of which is in the skeleton.

Total plasma phosphorus is about : 12 mg/dL

1. *Organic compounds* : two-thirds of the total plasma phosphorus.
2. *Inorganic phosphorus* : Remaining one-third; inorganic phosphorus (Pi) mostly in PO_4^{3-}, PO_4^{2-} and $H_2PO_4^-$.

The amount of phosphorus normally entering bone : is about 3 mg/kg/d (97 µmol/kg/d), with an equal amount leaving via reabsorption.

Aabsorption in GIT : Phosphorus is absorbed in the *duodenum* and *small intestine* by both *active transport* and *passive diffusion*. However, unlike the absorption of Ca^{2+} the absorption of Pi is linearly proportionate to dietary intake. Many stimuli that increase Ca^{2+} absorption, including 1,25-dihydroxycholecalciferol also increase Pi absorption.

Reabsorption in kidneys : The Pi in the plasma is filtered in the glomeruli, and 85-90% of the filtered Pi is reabsorbed. Active transport in the proximal tubule accounts for most of the reabsorption, and this active transport process is powerfully inhibited by parathyroid hormone.

(Ref. Ganong 22th edition, Page 382, 383)

Control of secretion of Parathormone by calcium ion concentration

The calcium ion concentration in the ECF is the main factor, which controlls the secretion of parathormone.

Increase Ca^{++} concentration decrease the rate of secretion of parathormone.

Decrease the Ca^{++} concentration causes increase the parathormone secretion. Beside these some other factor also controls the parathormone secretion.

These includes-

i. Excessive quantities of calcium in the diet.
ii. Increase vit-D in diet.
iii. Bone absorbtion caused by the factors other than parathormone.

(Ref. Guyton & Hall-11th ed; page-988)

Vitamin D

Vit-D plays an important role in Ca^{++} absorption from the GIT and it also has important effect on bone deposition and bone reabsorption.

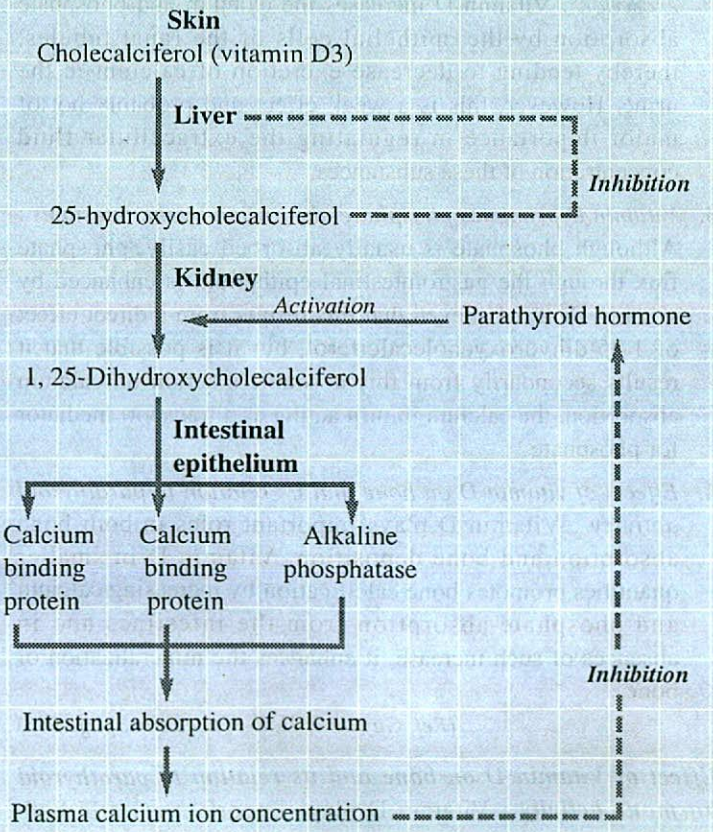
Formation of 1,25-dihydroxycholecalciferol : Vitamin D_3 (also called cholecalciferol) is formed in the skin as a result of irridation of *7-dehydrocholesterol*, a substance normally in the skin, by ultraviolet ray's from the sun.

The first step in the activation of cholecalciferol is to convert it to 25-hydroxycholecalciferol in the liver.

Then in the 2nd step 25-hydroxycholecalciferol converted into 1,25-dihydroxycholecalciferol with the help of PTH in the kidney.

(Ref. Guyton & Hall-11th ed; page-983)

Activation of vitamin D_3 to form 1,25 dihydroxycholecalciferol and the role of vitamin D in the plasma calcium concentration *: (Ref. Guyton & Hall-11 edition; page 984)*



Actions of vitamin D

The active form of vitamin D, 1,25-dihydroxycholecalciferol, has several effects on the intestines, kidneys, and bones that increase absorption of calcium and phosphate into the extracellular fluid and contribute to feedback regulation of these substances.

1. *Hormonal effect of vitamin D to promote intestinal calcium absorption* : 1,25-dihydroxycholecalciferol itself functions as a type of *'hormone'* to promote intestinal absorption of calcium. It does this principally by increasing over a period of about 2 days, formation of a *calcium-binding protein* in the intestinal epithelial cells. This protein functions in the brush border of these cells to transport calcium into the cell cytoplasm, and the calcium then moves through the basolateral membrane of the cell by facilitated diffusion. The rate of calcium absorption is directly proportional to the quantity of this calcium-binding protein. Furthermore, this protein remains in the cells for several weeks after the 1,25-dihydroxychole calciferol has been removed from the body, thus causing a prolonged effect on calcium absorption.

   Other effects of 1,25-dihydroxycholecalciferol that mght play a role in promoting calcium absorption are the formation of- i. a calcium-stimulated ATPase in the brush border of the epithel ial cells and ii. an alkaline phosphatase in the epithelial cells. The precise details of all these effects are unclear.

2. *Vitamin D decreases the renal calcium and phosphate excretion* : Vitamin D increases the calcium and phosphate absorption by the epithelial cells of the ranal tubules, thereby tending to decrease excretion of calcium in the urine. However, this is a week effect and probably not of major importance in regulating the extracellular fluid concentration of these substances.

3. *Vitamin D promotes phosphate absorption by the intestines* : Although phosphate is usually absorbed easily, phosphate flux through the gastrointestinal epithelium is enhanced by vitamin D. It is believed that this results from a direct effect of 1.25-dihydroxycholecalciferol, but it is possible that it results secondarily from this hormone's action on calcium absorption, the calcium in turn acting as a transport mediator for phosphate.

4. *Effects of vitamin D on bone and its relation to parathyroid activiry* : Vitamin D plays important roles in both bone absorption and bone deposition. Vitamin D in smaller quantities promotes bone calcification by increasing calcium and phosphate absorption from the intestines and in absences of such increase, it enhances the mineralization of bone.

(Ref. Guyton & Hall-11th edition; page 985)

Effect of Vitamin D on bone and its relation to parathyroid hormone activity : Vitamin D plays important roles in both bone absorption and bone deposition. The administration of *extreme quantities* of vitamin D causes absorption of bone. In the absence of vitamin D, the effect of PTH in causing bone absorption is greatly reduced or even prevented. The mechanism of this action of vitamin D is not known, but it is believed to result from the effect of 1,25-dihydroxy-cholecalciferol to increase calcium transport through cellular membranes.

Vitamin D in smaller quantities promotes bone calcification. One of the ways in which it does this is to increase calcium and phosphate absorption from the intestines. However, even in the absence of such increase, it enhances the mineralisation of bone. Here again, the mechanism of the effect is unknown, but it probably also results from the ability of 1,25-dihydroxy-cholecalciferol to cause transport of calcium ions through cell membranes- but in this instance, perhaps in the opposite direction through the osteoblastic or osteocytic cell membranes.

(Ref. Guyton & Hall-11th edition; page 985)

Disorder of parathyroid gland

Disorders of parathyroid glands are :

1. *Hypoparathyroidism* : When secretion of parathyroid hormone is decreased. The clinical condition is - *Tetany.*
   Cause :
   i. Surgical removal of thyroid or parathyroid.
   ii. Disease of the parathyroids.

2. *Hyperparathyroidism* : Excessive secretion of parathyroid hormone. The clinical conditions- *Osteitis fibrosa cystica.*
   Cause :
   i. Hyperplasia of the gland or tumour.
   ii. Prolong administration of parathyroid extracts.

Tetany

Aetiology : There is an increased excitability of peripheral nerves due either to a low serum calcium or to alkalosis in which the proportion of the serum calcium in the ionised form is decreased, although the total calcium concentration remains unaltered. Magnesium depletion should also be considered as a possible contributing factor, particularly in malabsorption. The most common cause of hypocalcaemia is a low serum concentration of albumin which does not result in tetany.

Causes of tetany :

1. Due to hypocalcaemia
   Malabsorption
   Osteomalacia
   Hypoparathyroidism
   Acute pancreatitis
   Chronic renal failure

2 Due to alkalosis
   Repeated vomiting of gastric juice
   Excessive intake of oral alkalis

Hyperventilation
Primary hyperaldosteronism.

* Coincident acidosis usually prevents tetany.

Clinical feature :

1. *In children :* a characteristic triad of carpopedal spasm, stridor and convulsions occurs, though one or more of these may be found independently of the others. The hands in carpal spasm adopt a characteristic position.The metacarpophalangeal joints are flexed, the interphalangeal joints of the fingers and thumb are extended and there is opposition of the thumb (main díaccoucheur). Pedal spasm is much less frequent. Stridor is caused by spasm of the glottis.
2. *Adult :* Complain of tingling in the hands, feet and around the mouth. Less often there is painful carpopedal spasm while stridor and fits are rare.

Adrenal Gland

Histological parts of adrenal gland : The adernal glands each of which weights about 4 gms, lie at the superior poles of the two kidney.

Histologically adrenal gland consist of two parts-

A. Outer : cortex.
B. Inner : medulla.

A. ***Cortex*** : Cortex form the main mass of the gland and divided into three distinct zone :
   i. *Outer zona glomerulosa* : It constitutes about 15 per cent of the adrenal cortex. It secretes mineralocor ticoids such as *aldosterone*. The secretion of this cells is controlled mainly by the ECF concentrations of *angiotensin II* and *potassium,* both of which stimulates aldosterone secretion.
   ii. *Middle zona fasciculata* : It constitutes about 75 per cent of the adrenal cortex. It secretes the glucocor ticoids *cortisol* and *corticosterone*, as well as small amounts of *adrenal androgens* and *estrogens*. The secretion of these cells is controlled in large part by the hypothalamic-pituitary axis via *adreno-corticotropic hormone (ACTH).*
   iii. *Inner zona reticularis* : It secretes the adrenal androgens *dehydroepiandrosterone (DHEA)* and *androstenedione,* as well as small amounts of *estrogens* and some *glucocorticoids*. ACTH also regulates secretion of these cells, although other factors such as *cortical androgen-stimulating hormone,* released from the pituitary, may also be involved.

B. ***Medulla*** : Medulla is the central 20 per cent of the glands, fuctionally related to the sympathetic nervous system. It secretes the hormones *epinephrine* and *nor epinephrine* and *dopamine* in response to sympathetic stimulation.

(Ref. Guyton & Hall-11th edition, page 944)

Classification of adrenal hormone

1. *On the basis of site of origin :*
   i. Adrenocortical hormone : These hormone again divides into three group ;
      a. Mineralocorticoids
      b. Glucocorticoids
      c. Sex hormones.
   ii. Medullary hormone : Epinephrine, norepine-phrine.
2. *On the basis of nature of hormone* :
   i. Steroid in nature : Cortical hormone e.g aldosterone, glucocorticoides or cortisol, sex hormones.
   ii. Derivatives of amino acid-Medullary hor-mone.

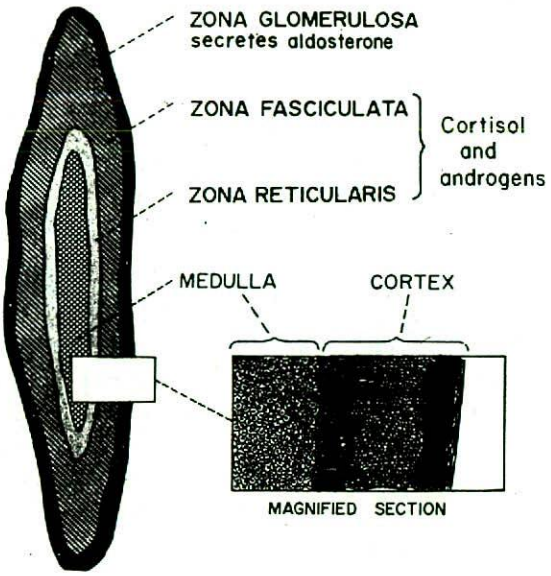


Fig. 8-15. *Secretion of adrenocortical hormones by different zones of the adrenal cortex.*

Adrenal medullary hormone

Structure and function of medullary hormone :

Nonepinephrine is formed by hydroxylation and decarboxy-lation of tyrosine, and epinephrine by methylation of norepinephrine. *PhenylethanolamineN-methyltransferase (PNMT)*, the enzyme that catalyzes the formation of epinephrine from norepinephrine, is found in appreciable quantities only in the *brain* and the *adrenal medulla*. Adrenal medullary PNMT is induced by glucocorticoids. Although relatively large amounts are required, the glucocorticoid concentration is high in the blood draining from the cortex to the medulla. After hypophysectomy, the glucocorticoid concentration of this blood falls and epinephrine synthesis is decreased.

In plasma, about 95% of the dopamine and 70% of the norepinephrine and epinephrine are conjugated to sulfate . Sulfate conjugates are inactive, and their function is unsettled.

Normal plasma level of adrenal medullary hormone :

1. *Norepinephrine* : In recumbent humans, the normal plasma level of free norepinephrine is about 300 pg/mL (1.8 nmol/L). There is a 50-l00% increase upon standing. The plasma norepinephrine level is generally unchanged after adrenalectomy
2. Free *epinephrine* level, which is normally about 30 pg/mL (0.16 nmol/L), falls to essentially zero after adrenalectomy. The epinephrine found in tissues other than the adrenal medulla and the brain is for the most part absorbed from the bloodstream rather than synthesized in situ. Interestingly, low levels of epinephrine reappear in the blood some time after bilateral adrenalectomy, and these levels are regulated like those secreted by the adrenal medulla. They may come from cells such as the ICA cells, but their exact source is unknown.
3. The plasma *free dopamine* level is about : 35 pg/mL (0.23 nmol/L), and there are appreciable quantities of dopamine in the urine. Half the plasma dopamine comes from the adrenal medulla, whereas the remaining half presumably comes from the sympathetic ganglia or other components of the autonomic nervous system.

Half-life of adrenal medullary hormone : The catecholamnines have a half-life of about 2 minutes in the circulation. For the most part, they are methoxylated and then oxidized to 3-methoxy-4-hydroxymandelic acid (vanillylman -delic acid, VMA;). About 50% of the secreted catecholamnines appear in the urine as free or conjugated metanephrine and normetanephrine, and 35% as VMA. Only small amounts of free norepinephrine and epinephrine are excreted.

Excretion of adrenal medullary hormone : In normal humans, about 30 μg of norepinephrine, 6 μg of epinephrine, and 700 μg of VMA are excreted per day.

(Ref. Ganong 22th edition, Page-358)

Epinephrine & norepinephrine

Receptors : The effects of norepinephrine and epinephrine are brought about by actions on two classes of receptors, α-and β-adrenergic receptors. Alpha receptors are subdivided into two groups, α_1 and α_2 receptors and β receptors into β_1, β_2 and β_3 receptors. There are three subtypes of α_1 receptors and three subtypes of α_2 receptors.

(Ref. Ganong 22th edition, Page-359)

Effects of epinephrine & norepinephrine : In addition to mimicking the effects of noradrenergic nervous discharge, *norepinephrine* and *epinephrine* exert-

1. Metabolic effects that include-
   a. Glycogenolysis in liver and skeletal muscle
   b. Mobilization of FFA
   c. Increased plasma lactate
   d. Stimulation of the metabolic rate.
2. *Effects on cardivascular system* :
   a. Norepinephrine and epinephrine both increase the force and rate of contraction of the isolated heart. These responses are mediated by β_1 receptors.
   b. The catecholarnines also increase myocardial excitability, causing extrasystoles and, occasionally, more serious cardiac arrhythmias.
   c. Norepinephrine produces vasoconstriction in most if not all organs via α_1 receptors.
   d. Epinephrine dilates the blood vessels in skeletal muscle and the liver via β_2 receptors. This usually overbalances the vasoconstriction produced by epinephrine elsewhere, and the total peripheral resistance drops.
   e. When norepinephrine is infused slowly in normal animals or humans, the systolic and diastolic blood pressures rise. The hypertension stimulates the carotid and aortic baroreceptors, producing reflex bradycardia that overrides the direct cardioacceleratory effect of norepinephrine. Consequently, cardiac output per minute falls.
   f. Epinephrine causes a widening of the pulse pressure. but because baroreceptor stimulation is insufficient to obscure the direct effect of the hormone on the heart, cardiac rate and output increase.
3. Catecholaimnes increase alertness. Epinephrine and norepinephrine are equally potent in this regard, although in humans epinephrine usually evokes more anxiety and fear.
4. The catecholamines have several different actions that affect blood glucose. Epinephrine and norepinephrine both cause glycogenolysis. They produce this effect via β-adrenergic receptors that increase cAMP, with activation of phosphorylase, and via α-adrenergic receptors that increase intracellular Ca^{2+}.

   In addition. the catecholammes increase the secretion of insulin and glucagon via β-adrenergic mechanisms and inhibit the secretion of these hormones via α-adrenergic mechanisms.
5. When injected. epinephrine and norepinephrine cause an initial rise in plasma K^+ because of release of K^+ from the liver and then a prolonged fall in plasma K^+ because of an increased entry of K^+ into skeletal muscle that is mediated by β_2-adrenergic receptors. There is some evidence that activation of α receptors opposes this effect. Thus, the

catecholamines may play a significant role in regulating the ratio between extracellular and intracellular K^+.

(Ref. Ganong 22th edition, Page-359, 360)

Effects of Dopamine : The physiologic function of the dopamine in the circulation is unknown.

1. Injected dopamine produces renal vasodilation, probably by acting on a specific dopaminergic receptor.
2. It also produces vasodilation in the mesentery. Elsewhere, it produces vasoconstrction, probably by releasing norepinephrine.
3. It has a positively inotropic effect on the heart by an action on β_1-adrenergic receptors.
4. The net effect of moderate doses of dopamine is an increase in systolic pressure and no change in diastolic pressure. Because of these actions, dopamine is useful in the treatment of traumatic and cardiogenic shock.

Dopatnine is made in the renal cortex, and there are appreciable amounts in the urine. It causes natriuresis and may exert this effect by inhibiting renal Na^+-K^+ ATPase.

(Ref. Ganong 22th edition, Page-366)

Regulation of adrenal medullary secretion

Neural control : Certain drugs act directjy on the adrenal medulla, but physiologic stimully affect medullary secretion through the nervous system. Catecholamine *secretion is low* in *basal states*, but the secretion of epincphnine and, to a lesser extent, that of norepinephrine is *reduced* even further *during* sleep.

Increased adrenal medullary secretion is part of the diffuse sympathetic discharge provoked in emergency situations, which Cannon called the "*emergency function of the sympathoadrenal system.*"

The metabolic effects of circulating catecholamines are probably important, especially in certain situations. The calorigenic action of catecholamines in animals exposed to cold is an example. Animals with denervated adrenal glands shiver sooner and more vigorously than normal controls when exposed to cold. The glycogenolysis produced by epinephrinc and norepinephrine in hypoglycemic animals is another example. *Hypoglycemia is a potent stimulus* to catecholamine secretion. Glucagon can substitute for catecholamines as a counterregulatory hormone, and vice versa, but if the secretion of both is blocked, insulin tolerance is markedly reduced.

(Ref. Ganong 22th edition, Page-361)

Adrenal Cortical Hormone

Chemistry of adrenocortical hormone : All these hormones are steroid in nature derived from cholesterol and each has a steroid nucleus in their structure.

Mineralocorticoid aldosterone has an *oxygen atom* bound at the number 18 carbon. The glucocorticoids cortisol has a *keto oxygen* on carbon number 3 and is hydroxylated at carbon numbers 11 and 21.

(Ref. Guyton & Hall-11th edition; page 944)

Mineralocorticoid Hormones

i.	*Aldosterone*	: very potent, account for about 90 per cent of all mineralocorticoid activity.
ii.	*Deoxycorticosterone*	: 1/30 as potent as aldosterone, but very small quantities secreted.
iii.	*Corticosterone*	: slight mineralocorticoid activity.
iv.	*9α -Fluorocortisol*	: synthetic, slightly more potent than aldosterone.
v.	*Cortisol*	: very slight mineralocorticoid activity, but large quantity secreted.
vi.	*Cortisone*	: synthetic, slight mineralocorticoid activity.

(Ref. Guyton & Hall-11th edition; page 945)

Origin of name of mineralocorticoides : Mineralocorticoids are so called because they specially affect eletrolytes of the ECF-Sodium and Potassium in particular.

(Ref. Guyton & Hall-11th edition; page 945)

Glucocorticoid Hormones

i.	Cortisol	: very potent, account for about 95 per cent of all glucocorticoid activity.
ii.	Corticosterone	: provides about 4 per cent of total glucocorticoid activity, but less potent than cortisol.
iii.	Cortisone	: synthetic, almost as potent as cortisol.
iv.	Prednisone	: synthetic, *four times* as potent as cortisol.
v.	Methylprednisone	: synthetic, *five times* as potent as cortisol.
vi.	Dexamethasone	: synthetic, *30 times* as potent as cortisol.

(Ref. Guyton & Hall-11th edition; page 947)

Origin of name of glucocorticoids : Glucocorticoids are so called because they exhibit an important effect in increasing the blood glucose concentration.

Mineralocorticoids- Aldosterone

Aldosterone is bound to protein to only a slight extent.

Half-life is short about : 20 minutes

The amount secreted is small about : 0.15 mg/day
Total plasma aldosterone level about : 0.006 µg/dL
: 0.17 nmol/L.

Metabolism of aldosterone : Much of the aldosterone is converted in the liver to the tetrahydroglucuronide derivative, but some is changed in the liver and in the kidneys to an 18-glucuronide. This glucuronide, which is unlike the breakdown products of other steroids, is converted to free aldosterone by hydrolysis at pH 1.0, and it is therefore often referred to as the "*acid-labile conjugate.*" Less than 1% of the secreted aldosterone appears in the urine in the free form. Another 5% is in the form of the *acid-labile conjugate*, and up to 40% is in the form of the tetrahydroglucuronide.

(Ref. Ganong 22th edition, Page 367)

Cellular mechenism of aldesterone action : The basic action of aldesterone on the tubular cells to increase transport of sodium is still not fully understood. However, the cellular sequence of events that leads to increased sodium reabsorption seems to be the following :

1. *First*, because of its lipid solubility in the cellular membranes, aldosterone diffuses readily to the interior of the tubular epithelial cells.
2. *Second*, in the cytoplasm of the tubular cells, aldosterone combines with a highly specific *cytoplasmic receptor protein*, a protein that has a stereomolecular configuration that allows only aldosterone or very similar compounds to combine with it.
3. *Third*, the *aldosterone-receptor complex* or a product of this complex diffuses into the nucleus, where it may undergo further alterations, finally inducing one or more specific portions of the DNA to form one or more types of messenger RNA related to the process of sodium and potassium transport.
4. *Fourth*, the messenger RNA diffuses back into the cytoplasm, where, operating in conjunction with the ribosomes, it causes protein formation. The proteins formed are a mixture of *i.* one or more enzymes and *ii.* membrane transport proteins that, all acting together, are required for sodium, potassium, and hydrogen transport through the cell membrane. One of the enzymes especially increased is ***sodium-potassium adenosine triphosphatase***, which serves as the principal part of the pump for sodium and potassium exchange at the *basolateral membranes* of the renal tubular cells. Another protein, perhaps equally important, is a *channel protein* inserted into the *luminal membrane* of the same tubular cells that allows rapid diffusion of sodium ions from the tubular lumen into the cell; then the sodium is pumped the rest of the way by the *sodium-potassium pump* located in the *basolateral membranes* of the cell.

Thus, aldosterone does not have an immediate effect on sodium transport; rather, this effect must await the sequence of events that leads to the formation of the specific intracellular substances required for sodium transport. About 30 minutes is required before new RNA appears in the cells, and about 45 minutes required before the rate of sodium transport begins to increase; the effect reaches maximum only after several hours.

(Ref. Guyton & Hall-11th ed, page 949)

Functions of aldosterone :

1. It increases the reabsorption of sodium from kidney tubule specially in the *principal cells of the collecting tubule* and, to a lesser extent, in the distal tubule and collecting duct.
2. It increases the excretion of potassium through DCT and CT.
3. It helps in the reabsorbtion of chloride along with sodium.
4. It increases the water reabsorption from kidney tubule along with sodium and increases ECF volume.
5. It causes reabsorption of sodium and chloride and excreation of potassium from ducts of sweat gland.
6. It increases the absorption of sodium from intestine.
7. Excess aldosterone increases extracellular fluid volume and arterial pressure but has only a small effect on plasma sodium concentration.
8. Excess aldosterone causes hypokalemia and muscle weakness; too little aldosterone causes hyperkalemia, and cardiac toxicity.
9. Excess aldosterone increases tubular hydrogen ion secretion, with resultant mild alkalosis.

(Ref. Guyton & Hall-11th ed, page 947, 948)

Regulation of aldosterone secretion :

The regulation of aldosterone secretion is so deeply intertwined with the- i. *regulation of extracellular fluid electrolyte concentrations*, ii. *extracellular fluid volume*, iii. *blood volume*, iv. *arterial pressure*, and v. *many special aspects of renal function* that it is difficult to discuss the regulation of aldosterone secretion independently of all these other factors. However, it is important to list here as well the more important points of aldosterone secretion control.

Four factors are known to play essential roles in the regulation of aldosterone. In the probable order of their importance, they are as follows :

1. Increased potassium ion concentration in the extracellular fluid *greatly increases* aldosterone secretion.
2. Increased activity of the renin-angiotensin system also *greatly increases* aldosterone secretion.
3. Increased sodium ion concentration in the extracellular fluid *very slightly decreases* aldosterone secretion.
4. ACTH from the anterior pituitary gland is necessary for aldosterone secretion but has little effect in controlling the rate of secretion.

Of these factors, *potassium ion concentration* and the *renin-angiotensin system* are by far the most potent in regulating aldosterone secretion.

1. *Potassium ion concentration* : A small percentage increase in potassium concentration can cause a several-fold increase in aldosterone secretion.
2. *Renin-angiotensin system* : Likewise, activation of the renin-angiotensin system, usually in response to diminished blood flow to the kidneys or to sodium loss, can cause a several-fold increase in aldosterone secretion.

In turn, the aldosterone acts on the kidneys- i. to help them excrete the excess potassium ions and ii. to increase the blood volume and arterial pressure, thus returning the renin-angiotensin system toward its normal level of activity. These feedback control mechanisms are essential for maintaining life.

3. *Sodium ion concentration* : By contrast, the effects of sodium ion concentration in controlling aldosterone secretion are usually minor. Nevertheless, a 10 to 20 per cent decrease in extracellular fluid sodium ion concentration, which occurs on rare occasions, can perhaps double aldosterone secretion.
4. *ACTH* : By contrast, the effects of ACTH in controlling aldosterone secretion are usually minor. In the case of ACTH, if there is even a small amount of ACTH secreted by the anterior pituitary gland, it is usually enough to permit the adrenal glands to secrete whatever amount of aldosterone is required, but total absence of ACTH can significantly reduce aldosterone secretion.

(Ref. Guyton & Hall-11th ed, page 950)

Q. ***Why mineralocorticoids or aldosterone is essential for life or why it is called life saving hormone?***

Ans. Total loss of adrenocortical secretion usually causes death within 3 days to 2 weeks unless the person receives extensive salt therapy or injection of mineralocorticoids. Without mineralocorticoids, *potassium ion concentration* of the extracellular fluid *rises markedly*, *sodium* and *chloride* are *rapidly lost* from the body, and the *total extracellular fluid volume* and *blood volume* become greatly reduced. The person soon develops diminished cardiac output, which progresses to a shocklike state, followed by death. This entire sequence can be prevented by the administration of aldosterone or some other mineralocorticoid. Therefore, the *mineralocorticoids* are said to be the acute "*lifesaving*" portion of the adrenocortical hormones. The glucocorticoids are equally necessary, however, allowing the person to resist the destructive effects of life's intermittent physical and mental "stresses".

(Ref. Guyton & Hall-11th ed, page 950)

Aldosterone escape : Aldosterone is one of the body's most powerful sodium-retaining hormones, only transient sodium retention occurs when excess amounts are secreted. An aldosterone-mediated increase in extracellular fluid volume lasting more than 1 to 2 days also leads to an increase in arterial pressure. The rise in arterial pressure then increases kidney excretion of both salt and water, called *pressure natriuresis* and *pressure diuresis*, respectively.

Thus, after the extracellular fluid volume increases 5 to 15 per cent above normal, arterial pressure also increases 15 to 25 mm Hg, and this elevated blood pressure returns the renal output of salt and water to normal despite the excess aldosterone. This return to normal of salt and water excretion by the kidneys as a result of pressure natriuresis and diuresis is called *aldosterone escape*.

Thereafter, the rate of gain of salt and water by the body is zero, and balance is maintained between salt and water intake and output by the kidneys despite continued excess aldosterone. In the meantime, however, the person has developed hypertension, which lasts as long as the person exposed to high levels of aldesterone.

(Ref. Guyton & Hall-11th ed, page 948, 949)

Glucocorticoids- Cortisol / Hydrocortisone

Functions of glucocorticoids :

1. *On carbohydrate metabolism :* increases blood glucose
   a. It stimulates the gluconeogenesis in liver,
   b. It decreases the peripheral utilization of glucose.
   c. It decreases the transport of glucose to the periphery.
   d. Ultimately it increases blood glucose.
2. *On protein metabolism :*
   a. It increases peripheral utilization of protein.
   b. It decreases the transport of amino acids to the cell.
   c. It converts the amino acids into glucose in liver.
   d. It decreases the synthesis of protein.
3. *On fat metabolism :*
   a. It increases the mobilization of fatty acid from adipose tissue.
   b. It promotes the conversion of fat to acetyl-CoA and subsequent utilization.
   c. It stimulates beta oxidation.
   d. It has a ketogenic effect.
4. Cortisol is important in resisting stress and inflammation.
5. ***Anti-inflammatory effects of high levels of cortisol*** : When large amount of cortisol are secreted or injected into a person, the cortisol has two basic anti-inflammatory effects :
   a. It can block the early stages of the inflammation process before inflammation even begins, or
   b. If inflammation has already begun, it causes rapid resolution of the inflammation and increased rapidity of healing.

Cortisols prevents the development of inflammation by stabilizing lysosomes and by other effects :

i. Cortisol stabilizes the lysosomal membranes
ii. Cortisol decreases the permeability of the capillaries
iii. Cortisol decreases both migration of white blood cells into the inflammed area and phagocytosis of the damaged cells.
iv. Cortisol supresses the immune system, causing lymphocyte reproduction to decreased markedly.
v. Cortisol lowers fever mainly because it reduces the release of interleukin-I from the white blood cells

Thus, cortisol has an global effect in reducing all aspects of the inflammatory process.

6. *Effect on allergy* : Cortisol block the inflammatory response to allergic reaction.
7. *Effect on immunity in infectious diseases* : Administration of large doses of cortisol causes significant atrophy of all the lymphoid tissue through out the body, which inturn decreases the output of both T cells and antbodies from the lymphoid tissues. As a result, immunity of the body is decreased.
8. *Effect on blood cells in infectious diseases* : Cortisol increases the production of red blood cells, the cause of wihch is unknown.

(Ref. Guyton & Hall-11th edition, page 951, 952, 953)

Permissive action *(of glucocorticoids)*

Small amounts of glucocorticoids must be present for a number of metabolic reactions to occur, although the glucocorticoids do not produce the reactions by themselves. This effect is called their *permissive action*. Permissive effects include the requirement for glucocorticoids to be present for glucagon and catecholamines to exert their calorigenic effects, for catecholamines to exert their lipolytic effects and for catecholamines to produce pressor responses and bronchodilation.

(Ref. Ganong 22th edition; page-369)

Regulation of cortisol secretion

The key to control of cortisol secretion is the excitation of the hypothalamus by different types of stress. Stress stimuli activate the entire system to cause rapid release of cortisol, and the cortisol in turn initiates a series of metabolic effects directed toward relieving the damaging nature of the stressful state. In addition, there is direct feedback of the cortisol to both the hypothalamus and the anterior pituitary gland to decrease the concentration of cortisol in the plasma at times when body is not experiencing stress. However, the stress stimuli are the prepotent ones; they can always break through this direct inhibitory feedback of cortisol, causing either periodic exacerbations of cortisol secretion at multiple times during the day or prolonged cortisol secretion in times of chronic stress.

Carcadian rhythm of glucocorticoid secretion : The secretory rates of CRF, ACTH and cortisol are high in the early morning but low in the late evening; the plasma cortisol level ranges

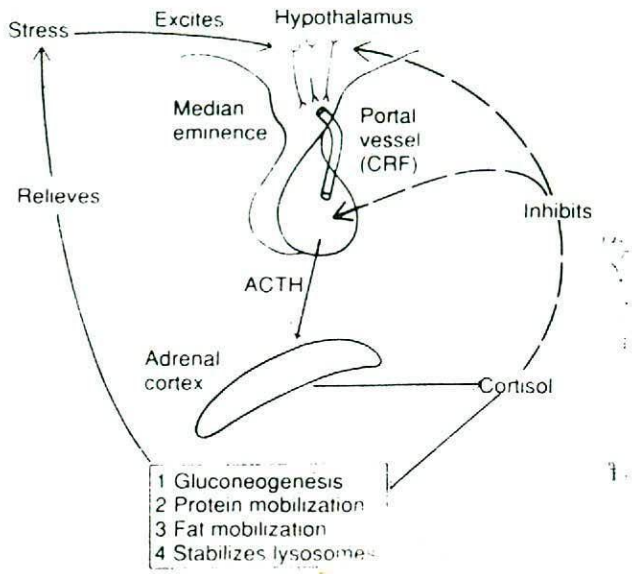


Fig. 8-16. *Mechenisms for regulation of glucocorticoid secretion.*

between a high of about 20 µg/dl an hour before arising in the morning and a low of about 5 µg/dl around midnight. This effect results from a 24 hour cyclical alteration in the signals from the hypothalamus that cause cortisol secretion. When a person changes daily sleeping habits, the cycle changes correspondingly.

Therefore, measurements of blood cortisol levels are meaningful only when expressed in terms of the time in the cycle at which the measurements are made.

(Ref. Guyton & Hall-11th edition, page 955)

Q. ***Why cortisol is called emergency homone?***

Ans. Any type of stress such as trauma, infection, intense heat or cold, surgical operations increases ACTH secretion, which within minutes greatly increases cortisol secretion. This cortisol causes rapid mobili-zation of fat and amino acids from cellular stores, making them available both for energy and for synthesis of other compounds including glucose and new proteins. So cortisol is called emergency hormone.

(Ref. Guyton & Hall-11th edition)

N.B If you are interested, please go through for-

1. Cellular mechenism of cortisol action.

(Ref. Guyton & Hall-11th edition, page 954)

2. Adrenal androgen- secretion & effects

(Ref. Guyton & Hall-11th edition, page 957)

Effects of adrenalectomy

i. Loss of appetite and vomitting.

ii. Loss of body wt, and wasting of limb muscles.
iii. Reduced ECF volume, blood volume, blood pressure & low CO.
iv. Increased retention of K^+, Hyperkalaemia.
v. Excessive loss of salts and water through kidney and diuresis occurs.
vi. Ultimately death in 5-7 days.

Disorders of adrenal cortex

Disorders of adrenocortical function may be of two types -

1. Lack of secretion i,e. hyposecretion of the adrenal cortex :
   It may be due to -
   i. Destruction of adrenal cortex (adrenal-ectomy).
   ii. Tuberculosis.
   iii. Lack of secretion of corticotropin from adenohypophysis.
   iv. Congenital failure of cortisol secretion with over secretion of other hormones.

   Two syndromes are encountered -
   a. *Acute adrenal insufficiency or Adrenal crisis :* Due to failure of cortisol secretion.
   b. *Chronic adrenal insufficiency :* Addison's disease.
2. Excess of secretion, i,e. hypersecretion of adrenal cortex : It results from over activity of the adrenal gland.
   a. *Cushing syndrome :* Due to over secretion of cortisol due to hyperplasia of zona fasciculata and reticularis.
   b. *Hyperaldosteronism :* Due to over secre-tion of aldosterone due to hyperplasia of zona glomerulosa. It is of two types -
      i. Primary aldosteronism
      ii. Secondary aldosteronism.
   c. *Adrenogenital syndrome :* Due to hyperplasia of zona reticularis.

Cushimg's Syndrome

Hyperfunction of the adrenal cortex causes a complex cascade of hormone effects called Cushing's syndrome. By far the most common cause is *iatrogenic*, due to prolonged immunosuppre-ssion with synthetic glucocorticoids such as prednisolone (chronic therapy e.g. for asthma).

Clinical features :

1. Weight gain is the most common symptoms and centripetal obesity is the most frequent sign .
   Features which have the best predictive value in favour of Cushing's syndrome in an obese patient are-
   a. Brushing
   b. Myopathy
   c. Hypertension.
2. Psychiatric disturbances : Usually depression is also the most common in Cushing's syndrome
3. Moon face
4. Hair thinning- Hursutism
5. Wasting and weakness of proximal thigh muscles.
6. Loss of height and back pain from compression fractures. May have exuberant callus with fracture. Osteoporosis.

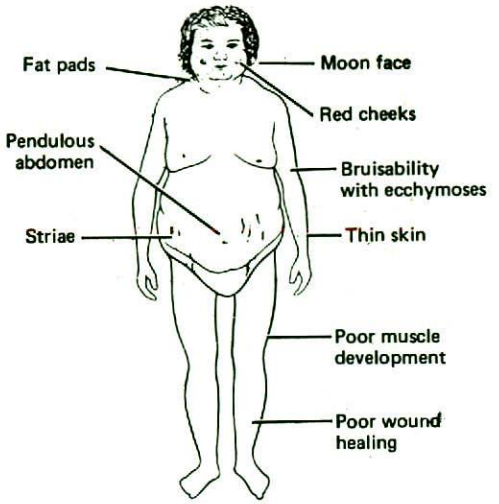


Fig. 8-17. *Typical findings in Cushing's syndrome.*

7. Menstrual disturbances.
8. Cataracts, mild exophthalmos.
9. Acne plethora
10. Tendency to infection with poor wound healing and inflammatory response.
11. Striae
12. Thin skin.

(Ref. Davidson's Principle and Practice of Medicine 18th ed; page-590)

Addision's Disease

Adddison's disease results from failure of the adrenal cortices to produce adrenocortical hormones, and this in turn is the most frequently caused by *primary atrophy* of the adrenal cortices. It is the hypofunctional state of adrenal cortex. *(Guyton 11th ed)*

Causes :

1. *Common*
   a. Autoimmune
      Sporadic
      Polyglandular syndromes
   b. Tuberculosis
   c. Bilateral adrenalectomy
2. *Rare* :
   a. Metastatic carcinoma, lymphoma
   b. Intra-adrenal haemorrhage (waterhouse-Friedrichsen syndrome following meningococcal septicaemia)
   c. Amyloidosis
   d. Haemochromatosis
   e. Adrenal infection other than tuberculosis (esp. AIDS).

(Ref. Davidson's Principle and Practice of Medicine 18th ed; page-590)

Clinical features :

1. *Glucocorticoid insufficiency*
   a. Weight loss
   b. Malaise
   c. Weakness
   d. Anorexia
   e. Nausea
   f. Vomitting
   g. Gastrointestinal- dirrhoea or constipation
   h. Postural hypotension
   i. Hypoglycaemia
2. Mineralocorticoid insuffiency
   a. Hypotension
3. Increased ACTH secretion
   a. Pigmentation
      i. Sun-exposed areas
      ii. Pressure areas, e.g. elbows, knees, palmar creases, knuckles, mucous membrane, conjunctivae, Recent scars
4. Loss of adrenal androgen
   Decrease in body hair, especially in female.

(Ref. Davidson's Principle and Practice of Medicine 18th ed; page-590)

Pheochromocytoma

It is a benign chromaffin cell tumor of the sympatho-adrenal system that produces catecholamines, i.e., norepinephrine and epinephrine.

Clinical features : It produces hypertension that may be paroxysmal in about half the patients. The patient will complain of attacks of producing headaches, sweating, palpitation, apprehension, flushing of the face, nausea, vomiting and tingling of the extremities.

Adrenal medullary tumours which secrete norepinephrine, or epinephrine or both, and produce sustained hypertension. However, 15% of epinephrine secreting tumours secrete this catecholamine episodically producing intermittent bouts of palpitations, headache, glycosuria and extreme systolic hypertension.

Treatment : Surgical removal of the tumor.

(Ref. Ganong 22th edition; page- 360)

Adrenogenital syndrome

Condition caused by excess secretion of androgenic hormones by the adrenal gland or by excess medication with male hormones. In congenital forms, the female infant may be considered erroneously to be male and the male child will have accelerated growth and penile enlargement. In acquired forms, masculine secondary sex characteristics appear in the female; and there is precious puberty in the male.

Pancrease

Physiologic anatomy of pancreas : Pancreas consist of two major types of tissues :

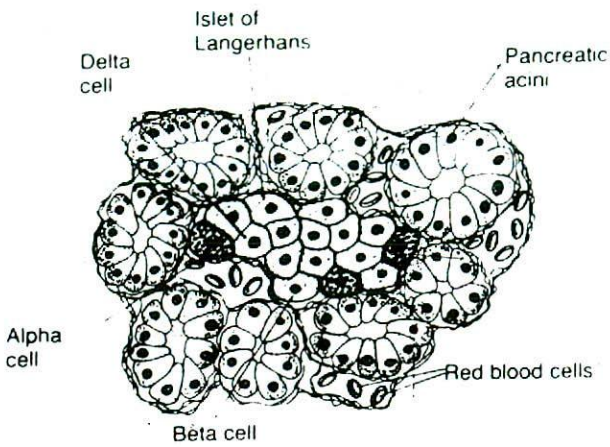


Fig. 8-18. *Physiological anatomy of Islets of langerhans in the pancreas.*

i. *The acini :* Which secretes digestive juice.

ii. *Islets of Langerhan's :* Which consist of different types of cells and secretes different hormone directly into the blood.

Cells of Islets :

1. Alpha (α) cell : Secretes glucagone.
2. Beta (β) cell : Secretes insulin.
3. Delta (δ) cell : Secretes somatostatin.
4. PP cell : Secrete pancreatic polypeptide.

These cells are distinguished from each other by their morphology and staining characteristic.

Alpha (α) cell constitute 25% of all cells,

Beta (β) cell constitute 60%,

Delta (δ) cell constitute 10%.

PP cell present in small number.

(Ref. Guyton & Hall-11th edition; page 961)

Insulin

Chemistry of insulin : Insulin is protein in nature with a molecular wt. of about 5,808. It is composed of two amino acid chains connected to each other by disulfide linkages. A chain contains 21 amino acid and B chain contain 30 amino acids. When the two amino acid chains are split apart the functional activity of insulin is lost.

(Ref. Guyton & Hall-11th edition; page 961)

Function of insulin

1. *On carbohydrate metabolism* : Insulin increases uptake, uses, storage of glucose by the liver, muscle and all the cells of the body and decreases blood glucose level as follows :

a. Insulin increases the activity of enzyme *glucokinase* which enhanced the uptake of glucose from blood and initiate phosphorilation of glucose in liver.
b. Insulin inhibits the enzyme *phosphorilase* thus prevents break down of liver glycogen.
c. Insulin stimulate the enzyme *glycogen synthetase* thus promotes glycogenesis.
d. Insulin promotes conversion of excess liver glucose into fatty acid.
e. Insulin inhibits gluconeogenesis.

2. *On fat metabolism :*
   a. Insulin promotes fatty acid synthesis.
   b. Insulin increases fat storage in the adipose tissue.
   c. Insulin act as fat sparer by increasing utilization of carbohydrate in presence of fat.

3. *On protein metabolism :*
   a. It increases the transport of amino acid to cells.
   b. It increases translation of m RNA on ribosome thus forming new protein.
   c. Insulin promotes the rate of transcription of DNA to form RNA, which increases protein synthesis.
   d. Insulin inhibits gluconeogenesis.
   e. Insulin depressed protein catabolism.

(Ref. Guyton & Hall-11th edition; page 963, 964, 965)

Q. ***Write down the effect of insulin on glucose uptake in tissues in which it has been investigated?***

Ans.

1. *Tissues in which insulin facilitates glucose uptake :*
   i. Skeletal muscles
   ii. Cardiac muscles.
   iii. Smooth muscles
   iv. Adipose tissue.
   v. Leukocytes
   vi. Crystalline lens of the eye
   vii. Pituitary gland
   viii. Fibroblasts
   ix. Mammary gland
   x. Aorta
   xi. A cells of pancreatic islets.

2. *Tissues in which insulin does not facilitate glucose uptake :*
   i. Brain (Except part of hypothalamus)
   ii. Kidney tubules
   ii. Intestinal mucosa
   iv. Red blood cells.

Effects of insulin on various tissues

A. *On adipose tissue :*
   1. Increased glucose entry
   2. Increased fatty acid synthesis
   3. Increased glycerol phosphate synthesis
   4. Increased triglyceride deposition
   5. Activation of lipoprotein lipase
   6. Inhibition of hormone sensitive lipase
   7. Increased K^+ uptake.

B. *On muscle :*
   1. Increased glucose entry
   2. Increased glycogen synthesis
   3. Increased amino acid uptake
   4. Increased protein synthesis in ribosomes
   5. Decreased protein catabolism
   6. Decreased release of gluconeogenic amino acids
   7. Increased ketone uptake
   8. Increased K^+ uptake.

C. *On liver* :
   1. Decreased ketogenesis
   2. Increased protein synthesis
   3. Increased lipid synthesis
   4. Decreased glucose output due to decreased gluconeogenesis and increased glycogen synthesis.

D. *General* :
   1. Increased cell growth.

Principal actions of insulin :

A. *Rapid (seconds)* :
   1. Increased transport of glucose, amino acids, and K^+ into insulin-sensitive cells.

B. *Intermediate (minutes)* :
   1. Stimulation of protein synthesis
   2. Inhibition of protein degradation
   3. Activation of glycogen synthase and glycolytic enzymes.
   4. Inhibition of phosphorylase and gluconeogenic enzymes.

C. *Delayed (hours)* :
   1. Increase in mRNAs for lipogenic and other enzymes.

Control of insulin secretion

Insulin secretion is regulated by following ways-

1. *Blood glucose level :* Increased blood glucose level increases insulin secretion. As the concentration of blood glucose rise above 100mg/dl of blood, the rate of insulin secretion rises rapidly, reaching a peak some 10 to 30 times the basal level at blood glucose concentration between 400 and 600 mg/dl.
2. *Amino acids :* Addition of excess amino acids stimulate insulin secretion.

3. *GI tract hormones :* Some GI Tract local hormones gastrin, secretin, GIP, CCK-PZ etc, moderately stimulate insulin secretion.
4. *Some other hormones of autonomic nervous system :* Glucagon, growth hormone, cortisol, and to a lesser extent, progesterone and estrogen either directly stimulate insulin secretion or potentiate the glucose stimulus for insulin secretion.

   Under some conditions, stimulation of the parasympathetic nerves to the pancrease can increase insulin secretion. However it is doubtful that this effect is of physiological significance for regulating insulin secretion.

(Ref. Guyton & Hall-11th edition; page 968)

Factors affecting insulin secretion

A. *Factors or conditions that increase insulin secretion* :
   1. Increased blood glucose
   2. Increased blood free fatty acids
   3. Increased blood amino acids
   4. Gastrointestinal hormones (Gastrin,cholecystokinin, secretin, gastric inhibitory peptide)
   5. Glucagon, growth hormone, cortisol
   6. Parasympathetic stimulation; acetylcholine
   7. Insulin resistance, obesity
   8. Sulfonylurea drugs (glyburide, tolbutamide).

(Ref. Guyton & Hall-11th edition; page 968)

B. *Factors or conditions that decrease insulin secretion* :
   1. Decreased blood glucose
   2. Fasting
   3. Somatostatin
   4. Catecholamines (α-agonist).

(Ref. Guyton & Hall-11th edition; page 968)

Insulinoma- Hyperinsulinism

Although much rarer than diabetes, excessive insulin production occasionally occurs from an adenoma of an islet of Langerhans.

About 10 to 15 per cent of these adenomas are malignant, and occasionally metastases from the islets of Langerhans spread throughout the body, causing tremendous production of insulin by both the primary and the metastatic cancers.

Indeed, more than 1000 grams of glucose has had to be administered every 24 hours to prevent hypoglycaemia in some of these patients.

(Ref. Guyton & Hall-11th edition; page 976)

Insulin shock and hypoglycaemia

The central nervous system normally derives essentially all its energy from glucose metabolism, and insulin is not necessary for this use of glucose. However, if high levels of insulin cause blood glucose to fall to low values, the metabolism of the central nervous system becomes depressed.

Consequently, in patients with insulin-secreting tumours or in patients with diabetes who administer too much insulin to themselves, the syndrome called *insulin shock may occur as follows* :

i. As the blood glucose level falls into the range of 50 to 70 mg/100 ml, the central nervous system usually becomes *quite excitable*, because this degree of hypoglycaemia sensitizes neuronal activity. Sometimes various forms of *hallucinations* result, but more often the patient simply experiences extreme nervousness, trembles all over, and breaks out in a sweat.
ii. As the blood glucose level falls to 20 to 50 mg/100 ml, clonic seizures and loss of consciousness are likely to occur. As the glucose level falls still lower, the seizures cease and only a state of *coma* remains.

Indeed, at times it is difficult by simple clinical observation to distinguish between diabetic coma as a result of insulin-lack acidosis and coma due to hypoglycaemia caused by excess insulin. The acetone breath and the rapid deep breathing of diabetic coma are not in hypoglycaemic coma.

Treatment :

i. Immediate intravenous administration of large quantities of *glucose*. This usually brings the patient out of shock within a minute or more.
ii. Administration of *glucagon* (or less effectively *epinephrine*) can cause glycogenolysis in the liver and thereby increase the blood glucose level extremely rapidly.

If treatment is not effected immediately, permanent damage to the neuronal cells of the central nervous system often occurs.

(Ref. Guyton & Hall-11th edition; page 976)

Glucagon

Function of glucagon

A. *Effects on glucose metabolism* : The major effects of glucagon on glucose metabolism are-
   a. Breakdown of liver glycogen (*glycogenolysis*)
   b. Increased *gluconeogenesis* in the liver.

   Both of these effects greatly enhance the availability of glucose to the other organs of the body.

   Break down of liver glycogen (glycogenolysis) : Glucagon helps glycogenolysis and increase blood glucose level as follows :
   1. It activates *adenyl cyclase* in the hepatic cell membrane.
   2. Which causes the fomation of *cyclic AMP.*
   3. Which activates *protein kinase regulator protein.*
   4. Which activates *protein kinase.*
   5. Which activates *phosphorylase b kinase.*

6. Which converts *phosphorylase b* into *phosphorylase a.*
7. Which promotes the degradation of glycogen into glucose-1 phosphate.
8. Which then dephosphorylated; and the glucose is released from the liver cells.

Glucagon increases gluconeogenesis :

a. Increases the rate of amino acid uptake by the liver cells and then conversion of many of the amino acid to glucose by *gluconeogenesis.*

B. *Other effects of glucagon* : Most of the other effects of glucagon occur only when its concentration rises well above the maximum normally found in the blood.

1. Perhaps the most important effect is that glucagon *activates adipose cell lipase,* making increased quantities of fatty acids available to the energy systems of the body.
2. It also inhibits the the *storage of triglycerides* in the liver, which prevents the liver from removing fatty acids from the blood; this also helps make additional amounts of fatty acids available for the other tissues of the body.

Glucagon in very large concentration also-

a. Enhances the strength of the heart.
b. Increases blood flow in some tissues, especially by the kidneys.
c. Enhances bile secretion.
d. Inhibits gastric acid secretion.

All these effects are probably of minimum importance in the normal function of the body.

(Ref. Guyton & Hall-11th edition; page 970)

Regulation of glucagon secretion

1. *Increased blood glucose inhibit glucagon secretion :* Decreased blood glucose level increases glucagon secretion and increased blood glucose level conversly inhibit glucagon secretion.
2. *Increased blood amino acids stimulate glucagon secretion* : High concentration of amino acids, as occur in the blood after a protein meal (specially the amino acids *alanine* and *arginine*) stimulate secretion of glucagon.

   The importance of amino acid stimulation of glucagon secretion is that the glucagon then promotes rapid conversion of the amino acids to glucose, thus making even more glucose available to the tissue.
3. *Exercise stimulate glucagon secretion* : In exhaustive exercise, the blood concentration of glucagon often increases fourfold to fivefold.

(Ref. Guyton & Hall-11th edition; page 971)

Factors affecting glucagon secretion

A. *Stimulatos :*

1. Amino acids (particularly the glucogenic amino acids : alanine, serine, glycine, cysteine, threonine)
2. CCK, gastrin
3. Cortisol
4. Exercise
5. Infections
6. Other stresses
7. Beta adrenergic stimulators
8. Theophylline
9. Acetylcholine.

B. *Inhibitors :*

1. Glucose
2. Somatostatin
3. Secretin
4. FFA
5. Ketones
6. Insulin
7. Phenytoin
8. Alpha adrenergic stimulators
9. GABA.

(Ref. Ganong 22th edition, Page 349)

Somastotin

Somatostatin inhibits glucagon and insulin secretion : The delta cells of the islets of Langerhans secrete the hormone somatostatin, a polypeptide containing only 14 amino acids that has an extremely short half-life of only 3 minutes in the circulating blood.

Almost all factors related to the ingestion of food stimulate somatostatin secretion. They include-

1. Icreased blood glucose
2. Increased amino acids
3. Increased fatty acids
4. Increased concentrations of several of the gastrointestinal hormones released from the upper gastrointestinal tract in response to food intake.

In turn, somatostatin has multiple inhibitory effects as follows :

1. Somatostatin acts locally within the islets of Langerhans themselves to depress the secretion of both insulin and glucagon.
2. Somatostatin decreases the motility of the stomach, duodenutm, and gallbladder.
3. Somatostatin decreases both secretion and absorption in the gastrointestinal tract.

Putting all this information together, it has been suggested that the principal role of somatostatin is to extend the period of time

over which the food nutrients are assimilated into the blood. At the same time, the effect of somatostatin to *depress insulin* and *glucagon secretion* decreases the utilization of the absorbed nutrients by the tissues, thus preventing rapid exhaustion of the food and therefore making it available over a longer period of time.

It should also be recalled that somatostatin is the same chemical substance as *growth hormone inhibitory hormone*, which is secreted in the hypothalamus and suppresses anterior pituitary gland growth hormone secretion.

(Ref. Guyton & Hall-11th edition; page 971)

Normal blood sugar level

i. In a normal person, the blood glucose concentration is narrowly controlled, usually between 80 and 90 mg per 100 ml of blood in the fasting person each morning before breakfast.

ii. This concentration increases to 120 to 140 mg per 100 ml during the first hour or so after a meal.

iii. But, the feedback systems for control of blood glucose return the glucose concentration rapidly back to the control level, usually within 2 hours after the last absorption of carbohydrates.

iv. Conversely, in starvation, the gluconeogenesis function of the liver provides the glucose that is required to maintain the fasting blood glucose level.

(Ref. Guyton & Hall-11th edition)

Regulation of normal blood glucose level

Factors maintaining blood glucose level are :

1. Humoral
2. Hormonal
3. Nervous.

1. ***Humoral factors*** : It includes :
   - i. *Role of liver* : The liver acts as an important *blood glucose buffer system.*
     - a. When blood glucose level rises to very high, after a meal, 2/3 of glucose absorbed from gut is almost immediately stored in liver as glycogen.
     - b. When blood glucose level falls, liver releases glucose back into blood due to presence of glucose-6-phosphatase.
     - c. When glycogen reservoir diminishes, liver enhances gluconeogenesis.
   - ii. *Role of muscle* :
     - a. During increase blood glucose level : Promotes glycogenesis and oxidation of glucose in muscle.
     - b. During decrease blood glucose level : Muscle glycogen supplies glucose to blood by cori cycle. It can not serve as a direct source of blood glucose during hypoglycaemia due to absence of glucose-6-phosphatase.
     - c. During exercise : It promotes entry of glucose into muscle cell thus decreasing blood glucose level.
   - iii. *Role of kidney* :
     - a. During increase blood glucose level : When blood glucose level exceeds the renal threshold level, excess glucose is excreted in urine, thus decreases blood glucose level.
     - b. During decrease blood glucose level : Kidney possesses gluconeogenesis, thus increases blood glucose level.

2. ***Hormonal factors*** :
   - I. *Main regulatory hormone (Antidiabetogenic hormone)* :
     - i. *Insulin* : Decrease blood glucose level.
       - a. Increase glucose uptake from blood to all cells of the body
       - b. Increase glycolysis
       - c. Increase glycogenesis
       - d. Decrease glycogenolysis
       - e. Decrease gluconeogenesis.
   - II. *Main counter regulatory hormone (Diabeto- genic hormone)* :
     - i. *Glucagon* : *Increase blood glucose level*
       - a. Increase glycogenolysis
       - b. Increase gluconeogenesis.
     - ii. *Glucocorticoids* : Increase blood glucose level :
       - a. It stimulates the gluconeogenesis in liver,
       - b. It decreases the peripheral utilization of glucose.
       - c. It decreases the transport of glucose to the periphery.
     - iv. *Growth hormone* : Increase blood glucose level :
       - a. Decrase uptake and utilization of glucose.
     - v. *Epinephrine* : Increase blood glucose level
       - a. Increase glycogenolysis.
     - vi. *Thyroid hormones* : Increase blood glucose level :
       - a. Increase glycogenolysis
       - b. Increase gluconeogenesis.
     - vii. *ACTH* : *Increase blood glucose level*
       - a. Increase gluconeogenesis.

3. ***Nervous factor*** :
   1. Hunger sensation : Raises blood glucose level by taking food during hypoglycemia.
   2. Satiety : Inhibits hunger centre, there by decreases blood glucose.

Importance of blood glucose regulation :

1. Glucose is the only nutrient that normally can be used by the brain, retina, and germinal epithelium of the gonads in sufficient quantities to supply them optimally with their required energy. Therefore, it is important to maintain the blood glucose concentration at a sufficiently high level to provide this necessary nutrition.

2. Most of the glucose formed by gluconeogenesis during the interdigestive period is used for metabolism in the brain. Indeed, it is important that the pancreas not secrete any insulin during this time; otherwise, the scant supplies of glucose that are available would all go into the muscles and other peripheral tissues, leaving the brain without a nutritive source.
3. It is also important that the blood glucose concentration not rise too high for four reasons :
   i. *First*, glucose can exert a large amount of osmotic pressure in the extracellular fluid, and if the glucose concentration rises to excessive values, this can cause considerable cellular dehydration.
   ii. *Second*, an excessively high level of blood glucose concentration causes loss of glucose in the urine.
   iii. *Third*, this causes osmotic diuresis by the kidneys, which can deplete the body of its fluids and electrolytes.
   iv. *Fourth*, long-term increases in blood glucose may cause damage to many tissues, especially to blood vessels. Vascular injury, associated with uncontrolled diabetes mellitus, leads to increased risk for heart attack, stroke, end-stage renal disease, and blindness.

(Ref. Guyton & Hall-11th edition; page 972)

Diabetes

Diabetogenic hormone : Hormones increasing blood glucose level. These are :

i. Glucagon
ii. Cortisol
iii. GH
iv. Thyroid hormone
v. Epinephrine and norepinephrine.
vi. TSH
vii. ACTH.

The diabetogenic hormone generally increasing blood sugar level in the follwing ways :

i. By breaking down of liver glycogen.
ii. Increasing the gluconeogenesis.
iii. By increasing glycogenolysis.
iv. By decreasing peripheral utilization of glucose.
v. By decreasing the transport of glucose to the cell .
vi. By increasing the absorption of glucose from intestine.

Antidiabetogenic hormone : Hormones decreasing blood glucose level. This is-

Insulin : It decreases blood glucose level by-

a. Insulin increases the activity of enzyme glucokinase which enhanced the uptake of glucose from blood and initiate phospho-rilation of glucose in liver.
b. Insulin inhibits the enzyme phosphorilase thus prevents break down of liver glycogen.
c. Insulin stimulate the enzyme glycogen synthetase thus promotes glycogenesis.
d. Insulin promotes conversion of excess liver glucose into fatty acid.
e. Insulin inhibits gluconeogenesis.

Pituitary diabetes

Specific increase in secretion of GH or generalized increase in secretion of all anteior pituitary hormones cuase elevated blood glucose level. This condition is called pituitary diabetes.

Adrenal diabetes

Both the increased rate of gluconeogenesis and the moderate reduction in the rate of glucose utilisation by the cells cause the blood glucose concentrations to rise. The rise in blood glucose in turn stimulates secretion of insulin. The increased plasma levels of insulin, however, are not as effective in maintaining plasma glucose as they are under normal conditions. For reasons that are not entirely clear, high levels of glucocorticoid reduce the sensitivity of many tissues, especially skeletal muscle and adipose tissue, to the stimulatory effects of insulin on glucose uptake and utilisation. One possible explanation is that high levels of fatty acids, caused by the effect of glucocorticoids to mobilise lipids from fat depots, may impair insulin's actions on the tissues. In this way, excess secretion of glucocorticoids may produce disturbances of carbohydrate metabolism very similar to those found in patients with excess levels of growth hormone.

The increase in blood glucose concentration is occasionally great enough (50 per cent or more above normal) that the condition is called *adrenal diabetes*.

Administration of insulin lowers the blood glucose concentration only a moderate amount in adrenal diabetes- not nearly as much as it does in pancreatic diabetes- because the tissues are resistant to the effects of insulin.

(Ref. Guyton & Hall-11th edition; page 972)

Diabetes insipidus

Diabetes insipidus is the syndrome characterised by *polyuria* and *polydipsia* that results when there is a vasopressin (ADH) deficiency or when the kidney fail to respond to the hormone. More common in the young.

Types :

i. Central diabetes insipidus
ii. Nephrogenic diabetes insipidus.

Central diabetes insipidus *(Failure to produce ADH)* : An inability to produce or release ADH from the posterior pituitary can be caused by head injuries or infections, or it can be congenital. Because the distal tubular segments cannot reabsorb water in the absence of ADH, this

condition, called *central diabetes insipidus.*

Effects : Formation of a large volume of dilute urine, with urine volumes that can exceed 15 L/day.

Response : The thirst mechanisms, are activated when excessive water is lost from the body; therefore, as long as the person drinks enough water, large decreases in body fluid water do not occur. The primary abnormality observed clinically in people with this condition is the large volume of dilute urine. However, if water intake is restricted, as can occur in a hospital setting when fluid intake is restricted or the patient is unconscious for example, because of a head injury, severe dehydration can rapidly occur.

Nephrogenic diabetes insipidus *(Inability of the kidneys to respond to ADH)* : There are circumstances in which normal or elevated levels of ADH are present but the distal tubular segments cannot respond appropriately. This condition is referred to as *nephrogenic diabetes insipidus* because the abnormality resides in the kidneys.

Cause :

i. This abnormality can be due to either failure of the countercurrent mechanism to form a hyperosmotic renal medullary interstitium.

ii. Failure of the distal and collecting tubules and collecting ducts to respond to ADH.
Many types of renal diseases can impair the concentrating mechanism, especially those that damage the renal medulla. May be due to-
   a. Diuretics
   b. Certain drugs, such as lithium, tetracyclines can impair the ability of the distal nephron segments to respond to ADH.

Effects :

i. Large volumes of *dilute urine* are formed, which tends to cause *dehydration* unless fluid intake is increased by the same amount as urine volume is increased.

(Ref. Guyton & Hall-11th edition; Ganong 22th edition)

Diabetes Mellitus

Definition : Diabetes mellitus is a syndrome of impaired carbohydrate, fat, and protein metabolism caused by either lack of insulin secretim or decreased sensitivity of the tissues to insulin.

Types of diabetes mellitus : There are two general types of diabetes mellitus :

1. *Type I diabetes*, also called *insulin-dependent diabetes mellitus (IDDM)* : It is caused by lack of insulin secretion.
2. *Type II diabetes*, also called *non-insulin-dependent diabetes mellitus (NIDDM)* : It is caused by decreased sensitivity of target tissues to the metabolic effect of insulin. This reduced sensitivity to insulin is often referred to as *insulin resistance.*

Effects of diabetes mellitus : In both types of diabetes mellitus, metabolism of all the main foodstuffs is altered. The basic effect of insulin lack or insulin -resistance on glucose metabolism is to prevent the efficient uptake and utilization of glucose by most cells of the body, except those of the brain. As a result, *blood glucose concentration increases, cell utilization of glucose falls increasingly lower,* and *utilization of fats and proteins increases.*

(Ref. Guyton & Hall-11th edition; page 971)

Metabolic changes in type I diabetes : Hyperglycemia and ketoacidasis are the hallmarks of untreated diabetes mellitus.

i. *Hyperglycemia* is caused by increased hepatic production of glucose combined with diminished peripheral utilization.

ii. *Ketosis* results from increased mobilization of fatty acids from adipose tissue combined with accelerated hepatic synthesis of 3-hydroxybutyrate and acetoacetate.

iii. However, not all the fatty acids flooding the liver can be disposed of through oxidation or ketone body synthesis. Fatty acids are also converted to *triacylglycerol*, which is packaged and secreted in *VLDL.*

iv. Chylomicrons are synthesized from dietary lipids by the intestinal mucosal cells following a meal. Because lipoprotein degradation catalyzed by *lipoprotein lipase* in adipose tissue is low in diabetics, the plasma chylomicron and VLDL levels are elevated, resuting in ***hypertiglyceridemia.***

v. These metabolic changes result from a deficiency of *insulin* and a relative excess of *glucagon*, the latter playing a critical role in stimulating *gluconeogenesis* and *ketogenesis.*

(Ref. Lippincott's Illustrated Reviews of Biochemistry, 2nd Edition; page-297)

Chronic effects of diabetes : The long-standing elevation of blood glucose is widely believed (but not conclusively proved) to cause the *chronic complications of diabetes* :

i. Premature atherosclerosis
ii. Retinopathy
iii. Nephropathy
iv. Neuropathy.

Intensive treatment with insulin delays the onset and slows the progression of these long-term complications. The benefits of tight control of blood glucose outweigh the increased risk of severe hypoglycemia. How hyperglycemia causes the chonic complications of diabetes is unclear. In cells where entry of glucose is not dependent on insulin, elevated blood glucose leads to increased intracellular glucose and its metabolites. For example, increased intracellular sorbitol may contribute to the formation of cataracts. Further hyperglycemia may promote the

condensation of *glucose* (or *its metabolites*, particularly *Glyceraldehyde 3 phoshate*) with cellular *proteins*, in a reaction analogous to the formation of HbA_{1c}. These glycated proteins may mediate some of the early microvascular changes of diabetes.

(Ref. Lippincott's Illustrated Reviews of Biochemistry, 2nd Edition; page-297)

(Please see page 130 of Lippincott's Illustrated Reviews of Biochemistry for discussion of the sorbitol pathway).

Clinical characteristics of patients with type I and type II diabetes mellitus :

Features	*Type I*	*Type II*
Age at onset	Usually <20 years	Usually >30 years
Body mass	Low (wasted) to normal	Obese
Plasma insulin	Low or absent	Normal to high initially
Plasma glucagon	High, can be supressed	High, resistant to supression
Plasma glucose	Increased	Increased
Insulin sensitivity	Normal	Reduced
Therapy	Insulin	Thiazolidinedione, metformin, sulfonyl-ureas, insulin.

(Ref. Guyton & Hall-11th edition; page 975)

Q. 00. **What are the investigations used in clinical practice for diagonosis of diabetes mellitus?**

Ans. Investigations used in clinical practice for diagonosis of diabetes mellitus are :

i. *Fasting blood glucose (FBS) level* :
   a. Normal FBS : 4.5-5.6 mmol/L (70-110 mg/dl)
   b. Suspicious of diabetes : > 5.6 mmol/L
   c. Diabetic : > 6.7 mmol/L (120 mg/dl)

ii. *Random blood glucose RBS* : > 10 mmol/L (180 mg/dl).

iii. *Glucose tolerance test- OGTT* (2hrs after brekfast or 75 mg intake of glucose with 250-300 ml of water) : After taking glucose by mouth samples of blood are collected at half-hourly intervals for at least 2 hours and their glucose content is estimated.
   a. Normal : <7.8 mmol/L
   b. Diabetic : > 10 mmol/L.

iv. Urine R/M/E (sugar)

v. Serum urea and creatinin.

Pineal gland

The pineal gland *(epiphysis)*, believed by Descartes to be the seat of the soul, has at one time or another been regarded as having a wide variety of functions.

i. *Anatomy* : The pineal arises from the roof of the third ventricle under the posterior end of the corpus callosum and is connected by a stalk to the posterior commissure and habenular commissure. There are nerve fibers in the stalk, but apparently do not reach the gland.

   The pineal stroma contains neuroglia and parenchymal cells with features suggesting that they have a secretory function. Like other endocrine glands, the pineal has highly permeable fenestrated capillaries. In young animals and infants, the pineal is large, and the cells tend to be arranged in alveoli.

   It begins to involute before puberty, and, in humans, small concretions of calcium phosphate and carbonate (***pineal sand***) appear in the tissue. Because the concretions are radiopaque, the normal pineal is often visible on x-ray films of the skull in adults. Displacement of a calcified pineal from its normal position indicates the presence of a space-occupying lesion such as a tumor in the brain.

ii. *Function* : It is now known to secrete *melatonin*, and it may function as a timing device to keep internal events synchronized with the light-dark cycle in the environment.

(Ref. Ganong 21th Edition; page 462)

Difference between the different types of diabetes.

Pituitary diabetes	*Adrenal diabetes*	*Diabetes mellitus.*
1. Due to increased secretion of anterior pituitary.	1. Due to increased sceretion of glucocorticoid.	1. Due to lack of insulin.
2. Glucose utilization by the cell depressed.	2. Glucose utiliztion by the cell depressed.	2. No utilization of glucose by the cells.
3. Weakly insulin sensitive.	3. Moderately insulin sensitive.	3. Strongly insulin sensitive.

Comparison of two types of diabetes mellitus

	Insulin-dependent diabetes mellitus (IDDM)	*Non-insulin-dependent diabetes meliitus (NIDDM)*
Synonym	Type I; juvenile-onset diabetes	Type II : adult-onset diabetes
Age of onset	Usually during childhood or puberty	Frequently after age 35
Nutritional status at time of onset of disease	Frequentlv undernourished	Obesity usually present
Prevalence	10%-20% of diagnosed diabetics	80%-90% of diagnosed diabetics
Genetic predisposition	Moderate	Vety strong
Defect or deficiency	β-Cells destroyed, eliminating production of insulin	Inability of β-cells to produce appropriate quantities of insulin : *insulin resistance*
Ketosis	Common	Rare
Plasma insulin	Low to absent	Normal to high
Acute complications	Ketoacidosis	Hyperosmolar coma
Oral hypoglycemic drugs	Unresponsive	Responsive
Treatment with insulin	Always necessary	Usually not required.

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Directions : Write T for true & F for false against each of the following statement.

Introduction

Q. 01. **The essential glands are**
- T a. adrenal cortex
- T b. parathyroid gland
- F c. thyroid gland
- F d. adrenal medulla
- F e. ovary.

Q. 02. **The glands having both endocrine and non-endocrine functions are**
- T a. gonads
- T b. hypothalamus
- T c. pancreas
- F d. thyroid gland
- F e. anterior pituitary

Q. 03. **ECF volume is maintained by**
- T a. ADH,
- T b. aldoesterone.
- T c. osmolarity of plasma.
- T d. plasma K^+ level
- F e. oxytocin.

Q. 04. **Hormones are**
- T a. chemical substances
- T b. secreted into body fluids
- F c. devoid of physiological control effect
- F d. of five general classes
- F e. secreted only by one cell

Q. 05. **Mechenism of action of protein hormones**
- T a. activating c-AMP system
- T b. facilitating cellular protein synthesis
- T c. activating enzymes
- T d. modulating cell permeability.
- F e. reacting with the receptors present on the nuclear membrane

Q. 06. **Polypeptide or protein hormones are**
- T a. secreted by anterior and posterior pituitary glands
- T b. secreted by parathyroid glands
- T c. synthesized on the rough endoplasmreticulum
- T d. transported by exocytosis.
- F e. not secreted by pancreas

Q. 07. **The neuropeptide hormones are**
- T a. epinepbrine
- T b. antidiuretic hormone
- T c. oxytocin
- F d. thyroid releasing homone
- F e. somatomedin

Q. 08. **General hormone are**
- T a. thyroxin
- T b. growth hormone
- F c. secretin
- F d. epinephrin.
- F e. acetylecholine

Q. 09. **The local hormones are**
- T a. colecystokinin
- T b. gastrin
- T c. secretin
- F d. ACTH
- F e. TSH.

Q. 10. **Following are local hormones**
- T a. Insulin
- T b. gastrin
- F c. Heparin
- F d. Bradykinin
- F e. Acetyl choline

Q. 11. **Tropic hormone are**
- T a. LH.
- T b. TSH
- T c. FSH
- F d. Insulin
- F e. Epinephrin

Q. 12. **The hormone receptors are located in the**
- T a. nucleus.
- T b. surface of the cell membrane

F c. target organ
F d. cell cytoplasm
F e. organelles

Q. 13. **Hormones that act through gene activation are**
T a. estrogens
T b. testosterone.
T c. cortisol
T d. aldosterone
F e. glucose

Q. 14. **Cyclic AMP serves as a second messenger in the secretion**
T a. FSH
T b. Glucagon
T c. Epinephrine
F d. Estrogen
F e. All.

Q. 15. **Production of c-AMP from ATP requires**
T a. Adenylate cyclase
F b. ATP ase
F c. cAMP synthetase
F d. None
F e. All.

Q. 16. **Homiones that act through cAMP (second messen gers system) are**
T a. luteinizing hormone
T b. antidiuretic hormone.
T c. parathyroid hormone
F d. 1 ,25-dihydroxycholecalciferol
F e. progesterons

Q. 17. **Characteristics of cyclic AMP are**
T a. alters cell permeability
T b. causes protein synthesis
T c. activates enzymes
F d. activates neurotransmitter
F e. causes breakdown of membrane phospholipids.

Q. 18. **The second messenger systems include**
T a. calcium ion
T b. calmodulin.
T c. cAMP
T d. IP3
F e. phosphate ion

Q. 19. **Which hormone is not released following trauma**
T a. Thyroxine
F b. Glucagon
F c. ADH
F d. GH
F e. None.

Q. 20. **An adolescent desirous of increasing his muscle mass is advised to**
T a. Exercise the muscle
F b. Increase protein intake
F c. Take steroids
F d. Electrically stimulate the muscle
F e. None.

Q. 21. **All are seen in obesity except**
T a. Increased sensitivity to GH
F b. Diabetes
F c. Hyperuricemia
F d. Atherosclerosis
F e. All

Q. 22. **All are (may) seen in obesity**
T a. Diabetes
T b. Hyperuricemia
T c. Atherosclerosis
F d. Increased sensitivity to GH
F e. None.

Q. 23. **Energy for the brain in starvation is from**
T a. Glucose
T b. Ketones
F c. Fatty acids
F d. Amino acids
F e. None.

Q. 24. **Melatonin is secreted by**
T a. Pineal gland
F b. Hypothalamus
F c. Adrenal cortex
F d. Melanocytes
F e. None.

Hypothalamus

Q. 25. **Hypothalamus**
T a. secret releasing hormone which stimulates their target tissues through c-AMP
T b. secrets both releasing and inhibitory hormones
T c. synthesizes ADH and oxytocin.
F d. controls the secretion of parathyroid gland.
F e. is connected with posterior pituitary by hypothalamic hypophysial portal system.

Q. 26. **The hypothalamic releasing hormones**
T a. are transpoted by the hypothalamic hypophysial portal vessels in to the anterior pituitaiy
T b. are released in the median eminence
T c. stimulate the secretion of specific hormone from the anterior pituitary
F d. control posterior pituitary secretion

F e. have positive feedback reationship with posterior pituitary.

Q. 27. **Hypothalamic releasing hormone are**
T a. gonadothyrotropin releasing hormone.
T b. gonadotropin releasing hormone.
T c. growth hormone releasing hormone.
F d. prolactin inhibiting hormone.
F e. growth hormone inhibiting hormone.

Q. 28. **Osmoreceptors**
T a. are located in or near the hypothalamus.
T b. control the secretion of anti diuretic hormone.
T c. increase the discharge of impulses when body fluid osmolality is increased.
F d. are receptors for the actionof aldosterone
F e. become shrunken when ECF osmolatity decrease.

Q. 29. **Adrenocorticotropic hormone (ACTH)**
T a. stimulates the secretion of adrenal androgen
T b. is secreted from anterior pituitary
T c. stimulates the secretion of cortisol
F d. is a hypothalamic hormone
F e. is chemically steroid in nature.

Q. 30. **ACTH secretion is increased due to**
T a. severe trauma
T b. decreased blood cortisol level.
T c. increased secretion of corticotropin releasing hormone.
F d. decreased blood aldosterone.
F e. increased blood cholesterol level.

Q. 31. **Regarding ACTH the following statements are true except**
T a. It is not protein in nature
F b. Secreted by the basophil cells
F c. Controls secretion of adrenal cortex
F d. It can withstand heating up to 100 degree C
F e. All.

Q. 32. **FSH is secreted by**
T a. Basophils
F b. Chromophobes
F c. Acidophils
F d. Theca interna cells
F e. All.

Q. 33. **Function of leutenizing hormone is**
T a. Follicle maturation and ovulation
F b. Milk secretion
F c. Causes progesterone secretion during ovulation
F d. Maintains placenta
F e. None

Q. 34. **TRH stimulates TSH and ...**
T a. Prolactin
F b. GH
F c. Oxytocin
F d. Gonadotrophin
F e. All.

Q. 35. **The satiety centre is located in the**
T a. Ventromedian nucleus of hypothalamus
F b. Dorsomedian nucleus of hypothalamus
F c. Perifornical region
F d. Lateral hypothalamic area
F e. All.

Q. 36. **Hypothalamus regulates all except**
T a. Anticipatory rise in heart rate
F b. Food intake
F c. Temperature
F d. Hypophysis
F e. All.

Q. 37. **Hypothalamus regulates**
T a. Hypophysis.
T b. Food intake
T c. Temperature
F d. Anticipatory rise in heart rate
F e. All.

Q. 38. **Decreased hypothalamic function casues depressed levels of all of following homones *except***
T a. Prolactin
F b. Growth hormone
F c. TSH
F d. ACTH
F e. None.

Q. 39. **Decreased hypothalamic function casues depressed levels of the following homones**
T a. Growth hormone
T b. TSH
T c. ACTH.
F d. Prolactin
F e. All.

Q. 40. **One of the following is a function of hypothalamus**
T a. Homeostasis of temperature
F b. Swallowing
F c. Vomiting
F d. Respiration
F e. All.

Q. 41. **Circadian rhythm is controlled by**
T a. Hypothalamus
F b. Supra chiasmatic nucleus
F c. Thalamus
F d. Pineal gland
F e. None.

Q. 42. **The effect of hypophysectomy is**
- T a. Glucocorticoid deficiency
- T b. Mineralo corticoid deficiency
- T c. Menstrual failure
- T d. All
- F e. None.

Q. 43. **Osmoreceptors are present in**
- T a. Anterior hypothalamus
- F b. Internal carotid artery
- F c. Left atrium
- F d. Ventricle
- F e. All.

Pituitary

Q. 44. **The pituitary gland**
- T a. secretes prolactin.
- T b. is essential for life.
- T c. secretes anti-diuretic hormone.
- T d. secretion is under hypothalamic control.
- F es. regulates other endocrine glands.

Q. 45. **Beta endorphin is**
- T a. Hormone of the intermediate lobe of pituitary
- F b. A lipoprotein
- F c. Analogue of morphine
- F d. Morphine receptor in brain
- F e. All.

Q. 46. **Not a glycoprotein**
- T a. GH
- F b. FSH
- F c. LH
- F d. TSH
- F e. All.

Q. 47. **Effects of panhypopituitarism in the adult are**
- T a. loss of sexual function
- T b. hypothyroidism
- T c. decreased production of glucocorticoids
- F d. loss of weight
- F e. dwarfism.

Q. 48. **Panhypopituitarism causes all except**
- T a. Pigmentation
- F b. Infertility
- F c. Loss of secondary sexual characters
- F d. coid intolerance
- F e. None

Q. 49. **Panhypopituitarism causes all except**
- T a. Infertility
- T b. Loss of secondary sexual characters
- T c. coid intolerance
- F d. Pigmentation
- F e. All.

Anterior pituitary gland

Q. 50. **Hormones secreted from the anterior pituitary gland**
- T a. Growth hormone
- T b. Prolactin
- T c. TSH
- T d. ACTH
- F e. Somatostatin

Q. 51. **Secretion of anterior pituitary gland**
- T a. shows a negative feed back mechanism.
- T b. depends on the release of hypothalamic releasing hormone.
- T c. is independent of CNS control from above the level of the hypothalamus.
- F d. depends on direct neural connection with hypothala -mus.
- F e. depends on the plasma glucose level.

Q. 52. **The anterior pritutary hormones are**
- T a. luteinizing hormone
- T b. thyroid stimulating hormone
- T c. corticotropin
- F d. antidiuretic hormone
- F e. aldosterone.

Q. 53. **Growth hormone**
- T a. increases utilization of fat for energy
- T b. is a diabetogenic hormone.
- T c. causes mobilization of fatty acid from adipose tissue
- T d. decreases carbohydrate utilization
- F e. causes breakdown of protein

Q. 54. **Growth hormone**
- T a. is a diabetogenic hormone.
- T b. promotes positive nitrogen balance.
- T c. secretion is under hypothalamic control.
- T d. stimulates the liver to secrete somatomedins.
- F e. acts directly to cause bone and cartilage growth.

Q. 55. **Human growth hormone**
- T a. acts as a *protein sparer*.
- T b. causes ketosis.
- T c. is a small protein molecule.
- F d. comes from lactotropes.
- F e. acts as a *fat sparer*.

Q. 56. **Growth hormone secretion increases during**
- T a. hypoglycemia.
- T b. exercise and excitement.

T c. young age.
T d. starvation.
F e. low concentration of fatty acid in the blood

Q. 57. **In a person who has fasted for 5 days all are seen except**
T a. GH levels decreased
F b. Glucose tolerance decreased
F c. Immunoreactive insulin decreased
F d. Free fatty acids (plasma) increased.
F e. None.

Q. 58. **In a person who has fasted for 5 days seen**
T a. Glucose tolerance decreased
T b. Immunoreactive insulin decreased
T c. Free fatty acids (plasma) increased.
F d. GH levels decreased
F e. All.

Q. 59. **True about growth hormone is that**
T a. It causes diabetes mellitus resistant to insulin
F b. Causes hyperglycemia
F c. Enhances lipogenesis
F d. Causes hypoglycemia
F e. None.

Q. 60. **Impaired growth hormone secretion in children**
T a. can be effectively treated by human growth hormone.
T b. leads to short stature.
F c. causes mental retardation.
F d. causes delayed puberty.
F e. increases size of the soft tissue.

Q. 61. **Pituitary dwarfism**
T a. occurs when growth hormone level declines.
T b. is associated with proportionate growth and development
F c. is not associated with short strature.
F d. includes mental retardation.
F e. occurs during adulthood.

Q. 62. **Dwarfism occurs due to deficiency of**
T a. somatomedins.
T b. growth hormone
T c. thyroid hormone
F d. insulin
F e. adrenocortical hormone

Q. 63. **Features of acromegaly are**
T a. kyphosis.
T b. enlargement of liver and kidney.
T c. enlargement of tongue.
T d. enlargement of hands and feet.
F e. deficiency of somatostatin.

Q. 64. **Transection of pituitary stalk leads to increase in**
T a. Prolactin
F b. TSH
F c. GH
F d. ACTH
F e. All.

Q. 65. **Prolactin**
T a. secretion is regulated by hypothalamus.
T b. is responsible for initiation and maintinance of milk production.
T c. is a hormone of anterior pituitary.
F d. is responsible for breast growth at puberty.
F e. causes ejection of milk during suckling of breast.

Posterior pituitary gland

Q. 66. **Posterior pituitary gland**
T e. is called neurohypohysis.
T a. is composed of glial like cells i.e. pituicytes
T b. secretes hormone that binds with neurophysin.
F c. is a typical endocrine gland.
F d. secretes endorphin.

Q. 67. **Which is true regarding oxytocin**
T a. Secreted by para ventricular tissue
F b. Increased by stress
F c. Effective in males
F d. Important for maintaining pregnancy
F e. All.

Q. 68. **Oxytocin**
T a. causes contraction of myoepithelial cells and ejection of milk.
T b. causes contraction of uterus during labour.
T c. is a hormone of posterior pituitary.
F d. is formed mainly in the supraoptic nuclei.
F e. helps in development of breast.

Q. 69. **Oxytocin**
T a. reaches the posterior pituitary gland by hypothalamic hypophysial portal tract.
T b. is synthesized mainly by the paraventricular nucleus of the hypothalmus.
T c. causes contraction of the pregnant uterus at the time of parturition.
T d. concerned with ejection of milk
F e. is a steriod hormone.

Q. 70. **Oxytocin causes all except**
T a. Lactogenesis
F c. Contraction of uterine muscle
F b. Milk ejection
F d. Myoepithelial cell contraction.
F e. All.

Q. 71. **Oxytocin causes**
- T a. Contraction of uterine muscle
- T b. Milk ejection
- T c. Myoepithelial cell contraction.
- F d. Lactogenesis
- F e. All.

Q. 72. **Site of ADH action is**
- T a. Collecting tubule
- F b. Proximal tubule
- F c. Loop of Henle
- F d. Vasa recta
- F e. All.

Q. 73. **Antidiuretic hormone (ADH)**
- T a. decreases volume of urine.
- T b. deficiency causes diabetes insipidus.
- T c. at high concentration increases blood pressure.
- F d. is synthesized mainly by the paraventricular nucleus of the hypothalamus.
- F e. decreases reabsorption of water.

Q. 74. **Anti diuretic hormone (ADH)**
- T a. is mainly secreted from supraoptic nucleui.
- T b. secretion is regulated by osmoreceptor.
- T c. is a posterior pituitary hormone
- T d. increases reabsorption of water in the late distal tubules, colleting tubules and collecting duct
- F e. acts on proximal tubules.

Q. 75. **Anti-diuretic hormone is**
- T a. formed primarily in the supraoptic nuclei.
- T b. secreted when the osmolality of the body fluid is increased.
- F c. synthesized in the posterior pituitary.
- F d. stored in the hypothalamus.
- F e. increased during over hydration.

Q. 76. **Extracellular fluid volume is maintained by**
- T a. osmolarity of plasma.
- T b. plasma K^+ level.
- T c. ADH.
- T d. aldoesterone.
- F e. oxytocin.

Q. 77. **Oxytocin secretion promotes**
- T a. myometrial contraction.
- T b. myoepithetical cell contraction.
- T c. milk ejection.
- F d. lactogenesis.
- F e. galactopoiesis.

Thyroid gland

Q. 78. **Thyroid gland**
- T a. has effect on growth and development of CNS.
- T b. stimulates the oxidative metabolism in general.
- T c. stores thyroid hormones extracellularly.
- F d. can concentrate iodine.
- F e. is stimulated by hot.

Q. 79. **Thyriod gland**
- T a. the requirement of iodine is 1 mg/week to form normal quantities of thyroxine.
- T b. it secrets thyroxine, tri-iodothyronine and thyrocalci -tonin.
- F c. thyroxine is more potent than tri-iodothyronine.
- F d. duration of action of thyroxine is less than that of tri-iodothyronine.
- F e. thyroxine remains in free form in the blood.

Q. 80. **Thyroid cells**
- T a. provide necessary enzymes for oxidation of iodide
- T b. are cuboidal epithelial cells.
- T c. are concerend with iodide pump.
- T d. form thyroglobulin.
- F e. contain amino acid arginine.

Q. 81. **Thyroid hormones are**
- T a. almost absent in patients with myxedema
- T b. important for growth and development of fetalbrain.
- F c. protein in nature.
- F d. formed by conversion of ferrous iron into ferric form.
- F e. regulated by positive feedback mechanism

Q. 82. **Thyroid hormone secretion occurs**
- T a. when T_3 and T_4 levels are decreased.
- T b. when excessive cold occurs.
- F c. when T_3 and T_4 levels are increased.
- F d. at the time of emotion, excitement, stress etc
- F e. when sympathetic activity is increased.

Q. 83. **Thyroid hormones**
- T a. increase secretion of digestive enzyme
- T b. increase motility of GI tract.
- T c. increase BMR
- F d. decrease appetite
- F e. decrease metabolic rate

Q. 84. **The substances required for the biosynthesis of thyroxin are**
- T a. thyroglobulin
- T b. peroxidase
- T c. iodine
- F d. iron
- F e. cholesterol.

Q. 85. **Thyroxine**
- T a. Helps in the development of brain in the fetal period
- T b. secretion is regulated by TSR.

T c. increases the basal metabolic rate
F d. decreases the number and size of the mitochondira
F e. decreases the enzyme Na^+-K^+ ATPase

Q. 86. **Thyroxine binding globulin is increased in**
T a. Pregnancy
F b. Nephrotic syndrome
F c. Glucocorticod treatment
F d. Cancer chemotherapy.

Q. 87. **The most biologically active iodothyronine secreted by thyroid follicle is**
T a. T_3
F b. T_4
F c. RT_3
F d. thyroglobulin
F e. tri-iodothyroacetic acid.

Q. 88. **Tri-iodothyonine**
T a. is about four time potent than thyroxine.
T b. is metabolically active hormone of thyroid gland.
T c. is present in the blood in small quantities.
F d. persists for a longer time.
F e. is about 50% of thyroid hormones.

Q. 89. **Tri-iodothyronine (T_3)**
T a. is more potent than T_4.Q.
T b. has less affinity for binding protein.
F c. is secreted from the parafollicular cells of thyroid.
F d. is converted to T_4 in the body
F e. is less active than T_4

Q. 90. **Iodide is**
T a. absorbed from GIT into the blood.
T b. actively transported into the cell.
T c. required for the formation of thyroid hormone.
F d. required 100 mg/week.
F e. not dependent on TSH.

Q. 91. **Iodide trapping is**
T a. stimulated by TSH.
T b. taking place at the basal membrane of the thyroid cell.
T c. called iodide pump.
T d. an active process.
F e. stimulated by T_3 and T_4

Q. 92. **Tyrosine derivative hormones are**
T a. epinephrine
T b. thyroxine
T c. norepinephirine
F d. estrogen
F e. antidiuretic hormone.

Q. 93. **The hormones causing glycolysis are**
T a. T_3 and T_4
T b. insulin
F c. glucagon
F d. cortisol
F e. pancreatic polypeptid

Q. 94. **In hyperthyroidism there are**
T a. exopthalmos.
T b. tachycardia
T c. increased secretion of T_3 and T_4
F d. high level TSH in plasma
F e. may be weight gain

Q. 95. **In hyporthyroidism**
T a. during fetal life, infancy and child hood is known as cretinsim
T b. the concentration of TSH is high.
T c. there is deficiency of iodine
F d. the size of the thyroid gland is reduced
F e. blood cholesterol level is decreased

Q. 96. **A Patient with hypothyroidism is likely to have**
T a. Subnormal mouth temperature
T b. Tendency to fall alseep frequently
F c. Increased body hair
F d. Moist hands and feet.
F e. All.

Q. 97. **Total thyroidectomy leads to**
T a. increase TSH level
T b. increase blood cholesterol level
F c. exopthalmos
F d. diarrhea
F e. tachycardia.

Q. 98. **Myxedema**
T a. can be diagnosed by telephone.
T b. is associated with huskye voice
F c. causes blackish pigmentation all over the body.
F d. decreases the body weight.
F e. occurs in children.

Q. 99. **Regarding Myxoedema the following are true**
T a. Dullness, loss of memory
T b. Swollen, Oedematous look of the face
T c. Impotency, amenorrhoea etc
F d. BMR increased by 30-45%

Q. 100. **The common feature of hyperparathyroidism are**
T a. weight loss.
T b. BMR increased.
T c. increased T_3 and T_4 level in the blood.
F d. increased TSH level.
F e. intolerance to cold.

Q. 101. **Simple enlargement of thyroid gland is**

T a. due to deficiency of iodine
T b. called goiter
F c. due to deficiency of protein
F d. due to deficiency of tyrosine
F e. occured due to excessive secretion of T_3 and T_4.

Q. 102. **Calcitonin hormone is**
T a. a peptide hormone.
T b. secreted by thyroid gland.
F c. secreted by parathyroid gland.
F d. a steroid hormone.
F e. secreted by adrenal cortex.

Q. 103. **Calcitonin hormone**
T a. deceases plasma calcium concentration.
F b. increases plasma calcium concentration.
F c. has no effect on calcium concentration in ECF.
F d. has same effects of parathormone.
F e. increases sodium ion concentration.

Q. 104. **Calcitonin secretion is stimulated by**
T a. increased plasma calcium concentration.
F b. decreased plasma potassium concentration
F c. decreased Na^+ concentration.
F d. phosphate concentration.
F e. decreased by plasma calcium concentration

Q. 105. **Calcitonin is produced by**
T a. Thyroid
F b. Parathyroid
F c. Thymus
F d. Kidney
F e. All.

Parathyroid gland

Q. 106. **Parathyroid gland**
T a. regulates the Ca^{++} and PO_4^- metabolism in the body.
T b. is essential for life.
T c. secretes parathormone
F d. secretes calcitonin
F e. secretes calcitriol

Q. 107. **Parathormone**
T a. activates vitamin D
T b. enhances calcium absorption from the intestines
T c. acts by activating receptors on the cell membrane
F d. secretion is regulated by anterior pituitary gland
F e. enhances reabsorption of phosphate from renal tubules

Q. 108. **Parathormone**
T a. is a polypeptide
T b. controls calcium and phosphate concetration in ECF
F c. is not life saving hormone
F d. is a steroid hormone
F e. is tyrosine derivative.

Q. 109. **Parathormone**
T a. secretion is controlled by calcium ion concentration
T b. helps in calcium exchange between bone and ECF
T c. increases intestinal absorption of calcium
F d. decreases absorption of phosphate from intestine.
F e. helps in activation of vitamin-D.

Q. 110. **Parathormone**
T a. acts through second messenger
T b. increases blood calcium concentration
F c. is secreted by oxyphil cells of parathyroid gland
F d. decreases renal clearance of phosphate
F e. secretion rate is under control of hypothalamus

Q. 111. **Parathormone secretion regulator is**
T a. high level of phosphate in the plasma
T b. low ionized plasma Ca^{++} level
F c. high level of 1,25-dihydroxycholecalciferol
F d. vitamin D.
F e. low level of parathormone

Q. 112. **The site of action of parathormone**
T a. distal convulated tubules of kidney
T b. small intestine
T c. bone
F d. duct of salivary gland
F e. liver.

Q. 113. **Parathormone secretion is usually increased during**
T c. rickets
T d. lactation
T e. pregnancy.
F a. excessive intake of vitamin-D
F b. hypercalcemia

Q. 114. **Calcium in the plasma is**
T a. about 2.4 mmol/L.
T b. present in three forms
T c. combined with plasma protein
F d. about 80 percent diffusible
F e. about 50 percent non-diffusible

Q. 115. **Hormones concerned with calcium metaolism are**
T a. calcitonin.
T b. 1 ,25-dihydroxycholecalciferol.
T c. parathormone
F d. androgen.
F e. aldosterone

Q. 116. **Metastatic calcification occurs when calcium is in**

T a. Alkaline pH
F b. Acidic pH
F c. Neutral pH
F d. Ionic equilibrium
F e. All.

Q. 117. **Hypercalcemia**
T a. decreases the reflex activities
T b. occurs when calcium level is increased above normal
T c. depresses nervous system
F d. increases muscle activity
F e. causes diarrhea and increase of appetite.

Q. 118. **Hypocalcemia causes**
T a. nervous system excitement
T b. tetany
F c. depression in nervous system
F d. constipation
F e. lack of appetite.

Q. 119. **Calcium ion concentration is**
T a. controlled by parathyroid secretion
T b. 2.4 mEq/L in ECF
T c. decreased in rickets
F d. increased in pregnancy
F e. not controlled by parathyroid gland.

Q. 120. **1,25-dihydorxycholecalciferol**
T a. increases binding protien
T b. increases alkaline phosphatase
T c. is a steroid hormone
T d. increases calcium-stimulated ATP ase
F e. is formed in the liver.

Q. 121. **Vitamin D**
T a. increases calcium absorption from intestinal tract
T b. has effects on bone deposition
T c. helps in Ca^{++} absorption from bone.
F d. is converted to 1 ,25-dihydroxycholecalciferol in the liver
F e. is converted to 25-hydroxycholecalciferol in liver

Q. 122. **Vitamin-D**
T a. does not help in bone absorption and bone deposition
T b. causes transport of calcium ions.
T c. promotes intestinal calcium absorption
T d. promotes phosphate absorption by the intestines
F e. decreases renal calcium and phosphate excretion

Q. 123. **In hypoparathyroidism**
T a. tetanus develops
T b. bone usually remain strong.
T c. parathyroid glands do not secrete sufficient PTH.
F d. level of calcium in the body fluid increases
F e. calcium reabsorption from bone is increased

Q. 124. **Hypoparathyroidism is charaterized by**
T a. tetany
T b. hypocalcemia
T c. hyperphosphatemia.
F d. muscle weakness
F e. tetanic contraction of heart muscle.

Q. 125. **In hyperparathyroidism plasma Ca^{++} level is**
T a. increased
T b. 12 to 15 mg/dl
F c. 5 to7 mg/dl
F d. 9.4 mg/dl
F e. decreased.

Q. 126. **In hyperparathyriodism**
T a. constipation and abdominal pain occurs
T b. lack of appetite develops.
T c. depression of CNS occurs
F d. stimulation of peripheral nervous system occurs
F e. muscle weakness does not develop

Q. 127. **Ricket occures mainly**
T a. due to calcium and phosphate deficiency
T b. in children
F c. in old people
F d. due to deficiency of vitamin E
F e. in adult.

Q. 128. **Osteoporosis occurs due to**
T a. malnutrition
T b. deficiency of vitamin C
F c. lack of calcium in the bones
F d. premenopasual period
F e. Addison's disease.

Q. 129. **Weightlessness results in**
T a. Decreased osteoporosis
F b. Decreased cardiac output
F c. Hypotension
F d. Gut motility
F e. All.

Pancrease

Introduction

Q. 130. **Regarding islets of langerhans cells in the pancreas**
T a. there are 1-2 million cells in human pancreas.
T b. there are alpha, beta, delta and PP cells
F c. alpha cells are the most abundant cells
F d. they constitute exocrine part of the pancreas
F e. beta cells secretes glucagon

Q. 131. **An adult human pancreas has about**

T a. 250,000-750,000 islets
F b. 100-2000 islets
F c. 100,000-200,000 islets
F d. Above 1000,000 islets
F e. 1500-2000 islets

Q. 132. **Beta cells of pancreas produce**
T a. Insulin
F b. Glucagon
F c. Gastrin
F d. Pancreatin
F e. All.

Q. 133. **Increase in insulin receptors is seen in**
T a. Starvation
F b. Obesity
F c. Acromegaly
F d. Diabetes
F e. All.

Q. 134. **Amino acid sequence of human insulin differs from porcine insulin in**
T a. 1 amino acid
F b. 3 amino acids
F c. 5 amino acids
F d. None of the above
F e. All.

Q. 135. **The hormones causing glycolysis are**
T a. T_3 and T_4
T b. insulin
F c. glucagon
F d. cortisol
F e. pancreatic polypeptid

Q. 136. **The hormones regulating blood glucose concentration are**
T a. insulin
T b. cortisol
F c. ADH
F d. oxytocin
F e. calcitonin.

Insulin

Q. 137. **How many parts are there in insulin receptor** :
T a. 4
F b. 1
F c. 2
F d. 3
F e. 5

Q. 138. **Insulin stress test assay estimates**
T a. Growth hormone
F b. Diabetes mellitus
F c. Glucagon assay
F d. Catecholamines.
F e. All.

Q. 139. **Insulin**
T a. increases permeability to amino acid
T b. binds with its membrane receptor
T c. increases uptake of glucose by muscle cells and adapter cells
F d. causes more excretion of potassium ions.
F e. has diabetogenic effect.

Q. 140. **Insulin is**
T a. an anabolic hormone.
T b. a small protein
F c. a small peptide
F d. secreted from the delta cell of islets of langerhans
F e. a catabolic hormone

Q. 141. **Biphasic release of insulin secretion occurs**
T a. in basal fasting state
T b. after intravenous injection of 20 gm glucose
T c. in the second phase from a stable pool
F d. in the first phase from a stable pool
F e. in non-fasting state.

Q. 142. **The site of action of insulin is the**
T a. adipose tissue
T b. muscle.
T c. liver
F d. kidney
F e. brain

Q. 143. **Mechanisms of insulin to regulates glucose metabolism are**
T a. phosphorylation of glucose.
T b. polymerization of the monosaccharide units to form glycogen.
T c. inactivation of liver phophorylase
F d. decreasing the activity of glucokinase
F e. depressing the activity of glycogensyn thetase.

Q. 144. **Insulin stimulates the**
T a. translation of messenger RNA
T b. rate of transcription
T c. protein synthesis.
T d. transport of amino acid into the cells
F e. catabolism of protein

Q. 145. **Insulin secretion is regulated by**
T a. glucagon
T b. high blood glucose level
F c. adrenalin
F d. somatostatin.
F e. low blood glucose level

Q. 146. **Insulin secretion is increased by**

T a. gastrin
T b. excess blood glucose
F c. decreased concentration of amino acid
F d. somatostatin
F e. cholecystokinin.

Q. 147. **Lack of insulin is characterized by**
T a. glycosuria
T b. hyperglycemia
T c. cellular dehydration
F d. alkalosis
F e. water diuresis.

Q. 148. **Insulin deficiency causes**
T a. ketoacidosis
T b. lipolysis of stored fat
F c. drecreased free fatty acid
F d. increased utilization of acetoacetic acid
F e. decreased plasma cholesterol

Q. 149. **Insulin causes lipogenesis by**
T a. decreasing the free fatty acid in the blood
T b. inhibiting the enzyme hormone-sensitive lipase
F c. stimulating the enzyme hormone sensitive lipase
F d. the breakdown of adipose tissue
F e. inhibiting the lipoprotein lipase

Glucagon

Q. 150. **Glucagon**
T a. increases blood glucose level
T b. increases gluconeogenesis.
T c. is secreted by the alpha cells of the islets of Langerhans of pancrease
F d. is a steroid hormone
F e. decreases glycogenolysis

Q. 151. **Glueagon increases the blood glucose level by**
T a. glycogenolysis
T b. gluconeogenesis
T c. lipolysis.
F d. glycolysis
F e. glycogenesis

Q. 152. **Pancreatic glucagon**
T a. increases blood glucose concetration
T b. causes gluconeogensis and glycogenolysis
T c. acts through second messenger
F d. is a steroid hormone
F e. is produced by delta cells of islets of langerhans.

Somatostatin

Q. 153. **Somatostatin**
T a. is secreted by the delta cells of the islets of Langerhans of pancreas
T b. is a polypeptide
T c. depresses the secretion of both insulin and glucagon
F d. increases the motility of the stomach
F e. increases both secretion and absorption in the gastrointestinal tract.

Q. 154. **Delta cells of pancreas secrete**
T a. Somatostatin.
F b. Insulin
F c. Glucagon
F d. VIP
F e. All.

Q. 155. **Regarding somatostatin**
T a. they are also called insulin like growth factors.
T b. they are small proteins
T c. mainly synthesize in liver
T d. at least four somatomedins are isolated
F e. metabolic function of growth hormones exerted through somatostatin

Q. 156. **Somatostatin is produced by ..... cells of the pancreas**
T a. Delta
F b. Alpha
F c. Beta
F d. Acinar
F e. All.

Diabetes

Q. 157. **Diabetes mellitus is**
T a. of two types
T b. associated with increased blood glucose level.
T c. metabolic disorder
T d. caused by lack of insulin secretion
F e. not caused by decreased sensitibility of the tissues to insulin

Q. 158. **Blood glucose level is increased by**
T a. cortisol
T b. thyroid hormone.
T c. growth hormone
F d. insulin
F e. vit-D

Q. 159. **Increased blood glucose level causes**
T a. tissue injury
T b. increased utilization of fats
T c. loss of glucose in the urine
F d. over hydration
F e. increased storage of protein.

Q. 160. **Estimation of diabetes by**
T a. urinary glucose
T b. fasting blood glucose

T c. glucose tolerance test
T d. insulin level
F e. glucagon level

Q. 161. **Experimental diabetes is caused by**
T a. Alloxan
F b. PgE_1
F c. Radioactive yittrium
F d. Gold chloride
F e. All.

Q. 162. **Somyogi phenomenon is**
T a. Hypoglycemia followed by hyperglycemia
F b. Hyperglycemia followed by hypoglycemia
F c. Glycosuria with normal blood sugar
F d. Reactive hyperglycemia.
F e. All.

Q. 163. **Urinary osmolality in Diabetes Insipidus is**
T a. 300 mmol/Litre
F b. 100 mmol/Litre
F c. 150 mmol/Litre
F d. 900 mmol/Litre
F d. 500 mmol/Litre

Q. 164. **Hypertonic contraction of fluid volume is caused by**
T a. Diabetes Insipidus
F b. Addisons disease
F c. Cushings disease
F d. Salt losing nephropathy
F e. All.

Adrenal gland

Q. 165. **Life saving hormones are**
T a. parathyroid hormone
T b. aldosterone
F c. thyroid hormones
F d. growth hormone
F e. adrenocorticotropic hormone.

Q. 166. **Extracellular fluid volume is maintained by**
T a. ADH.
T b. aldoesterone.
T c. osmolarity of plasma.
T d. plasma K^+ level.
F e. oxytocin.

Q. 167. **Urinary osmolality in Diabetes insipidus is**
T a. 300 mmol/Litre
F b. 100 mmol/Litre
F c. 150 mmol/Litre
F d. 900 mmol/Litre
F c. 400 mmol/Litre

Q. 168. **Osmoreceptor is located at which site?**
T a. Anterior hypothalamus
F b. Renal medulla
F c. Carotid body
F d. Atrial chamber.
F e. All.

Q. 169. **In the adrenal gland, androgens are produced by the cells in the**
T a. Zona reticularis
F b. Zona glomerulosa
F c. Zona fasciculata
F d. Medulla
F e. All.

Q. 170. **Regarding ACTH the following statements are true except**
T a. It is not protein in nature
F b. Secreted by the basophil cells
F d. Controls secretion of adrenal cortex
F e. It can withstand heating up to 100 degree C
F e. All.

Q. 171. **The adrenal cortex**
T a. secretes cortisol
T b. secretes some androgens
F c. is not essential for life
F d. secretes calcitonin
F e. is under control of thyroid gland.

Q. 172. **Stimulator of the adrenal medulla to secrete epinephrine is**
T a. sympathetic nerve
F b. thyroid stimulating hormone
F c. ACTH
F d. corticotropin releasing hormone
F e. acetylecholine.

Q. 173. **The hormones secreted from adrenal gland are**
T a. epinephrine
T b. cortisol
T c. androgens
F d. calcitonin
F e. adrenocorticotropin.

Q. 174. **Sources of steroid hormone are**
T a. corpus luteum
T b. ovary
T c. testis
T d. adrenal cortex
F e. thyroid glands

Q. 175. **Steroid hormones**
T a. act through gene activation
T b. have cyclopentano-perhydrophenanthren nucleus.
T c. are synthesized from cholesterol.

F d. are secreted from hypothalamus
F e. act directly on target cell membrane

Q. 176. **Steroid hormones are**
T a. vitamin D
T b. aldosterone
T c. estrogen
F d. insulin
F e. calcitonin.

Q. 177. **Cortisol**
T a. Secretion increases following injury
F b. Favours protein synthesis
F c. Enhances effects of antigen-antibody reactions
F d. Tends to lower blood pressure

Q. 178. **Cortisol**
T a. causes gluconeogenesis
T b. has anti-inflammatory effect
T c. is synthesized from cholesterol
F d. is secreted from zona glumerulosa of adrenal cortex
F e. decreases blood glucose level.

Q. 179. **The permissive role of cortisol on other hormones are**
T a. glucagon
T b. catecholamine
F c. insulin
F d. growth hormone
F e. aectycholine.

Q. 180. **Aldosterone**
T a. is chemically steroid in nature
T b. is a life saving hormone.
T c. is an adrenocortical hormone
F d. secretion is controlled by osmoreceptor mechanism
F e. acts on blood vessels to increases blood pressure

Q. 181. **Excess aldosterone is associated with all except**
T a. Hyperkalemia
F b. Water retention
F c. Hypokalemia
F d. Hypertension
F e. All.

Q. 182. **Aldosterone**
T a. acts on the distal segment of renal tubule.
T b. secretion is increased during hyperkalemia .
F c. secretion is increased during hypernatremia
F d. secretion is decreased by the activation of renin angiotensin mechanism.
F e. is chemically protein in nature

Q. 183. **What is not true for aldosterone?**
T a. Is a polypeptide
F b. Secreted in increased amounts when blood volume falls
F c. Secretion tends to increase renal arterial rressure
F d. Secretion results in a reduction in uninary volume
F e. All.

Q. 184. **Adreno-cortical hormones**
T a. are called corticosteroids
T b. bind with receptor located in the cytoplasm
T c. are steroid hormones
F d. are protein in nature
F e. act through second messenger mechanism

Q. 185. **Aldosterone secretion is regulated by**
T a. sodium ion concentration in extracellular fluid
T b. ACTH secretion from the anterior pituitary.
T c. potassium ion concentration in extracelular fluid
T d. renin-angiotensin mechanism
F e. osmoreceptor mechanism

Q. 186. **Aldosterone secretion is increased by an increase in**
T a. renin secretion
T b. ACTH secretion
F c. red cell volume
F d. plasma pH
F e. plasma volume

Q. 187. **Reabsorption of Na^+ and excretion of K^+ especially in the collecting tubule is the function of**
T a. aldosterone
F b. cortisol
F c. norepinephrine
F d. anti-diuretic hormone
F e. steroid hormone

Q. 188. **The hyposecretion of adrenocortical hormone**
T a. causes addisons disease
T b. is associated with melanin pigmentation
T c. causes death resulting from cardiac arrest.
F d. is called addisonian crisis
F e. copes up the person in any adverse condition

Q. 189. **Adrenaline insufficiency causes**
T a. A fall in extracellular fluid volume
T b. Low blood pressure
F c. Increased breakdown of protein
F d. A rise in plasma sodium/potassium ratio
F e. All.

Q. 190. **Removal of adrenal glands will cause**
T a. decreased blood volume
T b. death in less than 2 weeks
F c. increased excretion of potassium
F d. increased blood pressure
F e. increased retention of sodium.

Q. 191. **All are seen in cushings syndrome except**
- T a. Hypoglycemia
- F b. Truncal obesity
- F c. Hypertension
- F d. Poor wound healing
- F e. All.

Q. 192. **In Cushing syndrome the following features are found**
- T a. Impotence with atrophy of testis
- T b. Rapidly increasing adiposity
- T c. Polycythaemia
- F d. Hypotension
- F e. All.

Q. 193. **Cushing syndrome**
- T a. is associated with increased blood glucose concentration
- T b. is associated with hypertension.
- T c. is associated with moon face
- T d. occurs in hypersecretion of cortisol
- F e. occurs due to excessive secretion of growth hormone

Q. 194. **Addison's disease**
- T a. present with hyponatremia and hyperkalemia
- T b. is characterised by melanin pigmentation of the mucous membrane
- T c. results from lack of adrenocortical hormones
- F d. presents with hyperglycemia
- F e. does not affcet the muscular activity.

Q. 195. **Addisons disease causes**
- T a. hypoglycemia
- T b. increase melanin formation and pigmentation.
- T c. hypokalemia
- F d. hypernatremia
- F e. alkalosis

Q. 196. **In addisons disease the following is seen**
- T a. Hyperkalemia
- F b. Hypernatremla
- F c. Hyperglycemia
- F d. High blood pressure
- F e. All.

Q. 197. **BMR is decreased in**
- T a. Addisons disease
- F b. Hyperthyroidism
- F c. Increased body temperature
- F d. Cushings syndrome
- F e. All.

Q. 198. **Primary aldosteronism**
- T a. is known as Conn's syndrome
- T b. is characterized by hypertension
- T c. is accompanied by hypokalaemia
- F d. is due to deficiency of aldosterone
- F e. shows high plasma renin level.

Q. 199. **Adrenogenital syndrome**
- T a. is diagnosed by urinary excretion of excess 17-keto steroid
- T b. occurs due to excessive secretion of androgens
- T c. causes masculinizing effect in female
- F d. is not associated with precocious puberty in male
- F e. occurs due to excessive secretion of cortisol.

9

Reproductive System

Reproduction

i. *Definition* : Reproduction is the process by which an individual produces its offspring.

ii. *Importance of reproduction :*
   a. To maintain own species in the world
   b. To increase the number for existance.

iii. *Types of reproduction* : It is of two types-
   a. *Asexual reproduction* : It occurs by simple division of unicellular organism.
   b. *Sexual reproduction* : It occurs by sexual contact of male and female. It occurs in higher animals.

Chromosome

i. *Definition* : Chromosomes are deeply stained thread like structures within the nucleus of each animal cell.

ii. *Chromosomes number* : 46 or 23 pairs
   a. Autosomes : 22 pairs
   b. Sexchromosomes : 1 pair (XX or XY).

iii. *Structure of chromosome* : Each choromosome is composed of a double helix of DNA along with histone and non-histone proteins. The DNA-protein complex exists as a highly coiled or folded structure.
   a. The *non-histone* proteins are DNA and RNA polymerases, gene regulatory proteins and HMG (high mobility group) proteins.
   b. The *histones* are the most abundant group of basic proteins which help packaging of chromosomal DNA. There are five histone proteins according to the concentration of arginine and lysine residues : H_1,H_2A, H_2B, H_3, and H_4.

iv. *Function* : Chromosomes act as carries of units of inheritance in the form of genes of nuclear DNA. Genes are borne by the chromosomes in linear series as parts of specific DNA molecules.

Sex

Man kind is divided into two sexes, the males and the females. What are the criteria by which this classification is made ?

There are four criteria :

i. Chromosomal (or genetic) sex
ii. Gonadal sex
iii. Phenotype sex
iv. Psychological sex.

Genetic (chromosomal) sex : If the chromosomal pattern is XX, the subject, no matter what is the outward appearance, is genetically a female. Conversely if the chromosomal pattern is XY, the subject is male (irrespective of the outer appearance). Hence XX and XY are female and male genotypes respectively.

Gonadal sex : Testes and ovaries are the male and the female gonads respectively. Therefore, when testes are present, the subject is gonadally, a male. Similarly, presence of the ovaries means that the subject is gonadally, a female.

Phenotype sex : By the accessory sex organs (penis, epididymis, vas, seminal vesicles and the prostate in the male and fallopian tube, uterus, vagina and vulva in the female) gender sex or the sex phenotype is determined. Thus female phenotype will have female accessory sex organs and the male phenotype will have male accessory sex organs.

Psychological sex : Psychological sex is the sex which the individual believes that he or she belongs to. Thus, if a girl from her infancy, is mistaken as a boy and is reared up among the boys and she thinks that she is a boy, her psychological sex is male.

In vast majority of cases, there is no confusion in sex characteristics, that is, in a male, the genetic, gonadal, phenotype and the psychological sex are all male; so is the case with the female. Rarely however, anomalous situation arises. Thus, someone may have a male genotype pattern of sex (XY) and yet the appearance from outwards (the external genitalia, the dress) may be of the female type and the subject believes that he is female.

Two terms are commonly used :

i. Sex determination
ii. Sex differentiation.

Sex determination

By the term sex determination, it is meant how the genetic sex patterns are made. Sex differentiation means the development of gonads, accessory sex organs and the psychological aspects of sex. Thus, sex determination occurs during the fertilization of the ovum. On the other hand, in the early weeks of intrauterine life, the gonadal and gender sex of the fetus are not differentiated. After a few weeks of intrauterine life, a fetal gonadal and gender sex differentiation (that is, outward sex differentiating features like the development of testes, penis, prostate etc. in males or ovary, uterus, vagina, vulva etc. in the female) occur.

Mechanism of sex determination : Human beings have 46 (23 pairs of) chromosomes of which 44 are autosomes and the rest two are sex chromosome. These two sex chromosomes in case of the female are XX, wheres in case of male, are XY. Therefore, the male and the female chromosomal pattern can be written as 44+XY(=46) and 44+XX (=46) respectively.

Owing to the reduction cell division (meiosis) a gamet (a spermatozoon or an unfertilized ovum) will contain 22 autosomes+1 sex chromosme. In case of an ovum it has to be (obviously) always 22+X, or 22+Y. Now during fertilization, one such spermatozoon and one such ovum unite to form a zygote. Therefore from the ovum the zygote is always getting 22 +X but from the spermatozoon it may get either 22+X or 22+Y.

When fertilization occurs, therefore, the zygotes chromosomal pattern (Karyotype) can be 44+XX or 44 + XY, and the genotype of the genetic sex of the zygote will be female (44+XX) or male (44+XY) respectively. Thus the spermatozon (not the ovum) is the sex determining factor.

Clinical determination of the sex in a given person

In some critical situation, it may be necessary (despite the outward apperance) to determine the sex of a given individual. For example, a so called woman athleteís phenotype may be female but genotype of a male and in the eyes of law the athlete is a male (and thus not eligible to compete in events exclusively meant for the females).

i. ***Genotype*** : In the epithelial cells of the female buccal cavity or vagina or leucocytes of the female, the nucleus may contain a chromatin mass which stains deeply with creayl violet, and has a diameter of about 1 mm. This is called Barr body. Presence of Barr body in the above mentioned cells indicates that the subject is genetically a female.

(In reality, Barr body says, there are at least XY chromosomes and more. Hence Barr body may also be seen in a Klinefelters syndrome).

ii. ***H-Y antigen-It's role in gonadal sex*** : On the chromosome a protein has been found out and is called H-Y antigen. It is now understood, that H-Y antigen is the key factor. If H-Y antigen is present, only then testis will develop in the fetus otherwise not. Thus, even in a fetus with a genothpe XY, if the H-Y antigen is missing there will be no formation of testis.

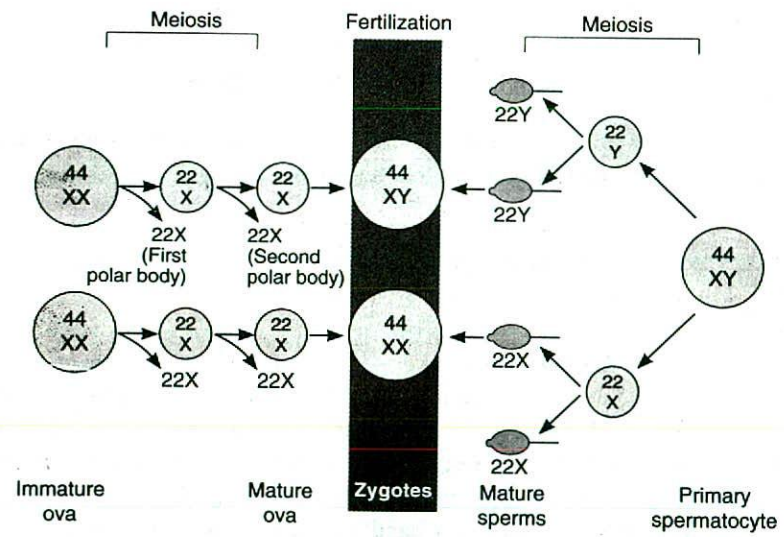


Fig. 9-1. Basis of genetic sex determination. In the two-stage meiotic division in the female, only one cell survives as the mature ovum. In the male, the meiotic division results in the formation of four sperms., two containing the X and two the Y chrosome. Fertilization thus produces a male zygote with 22 pairs of autosomes plus an X and a Y or a female zyggote with 22 pairs of autossomes and two X chromosomes.

Sex differentiation

Gonadal development : As stated earlier, when the Y chromosome and the H-Y antigen are present testes develop.

For the normal ovaries to be formed the fetus must have XX pattern.

Before the 6th week there is no gonadal development. Testes begin to be formed at the 7th week. Beginning of ovarian development occurs at the 9th week.

Phenotype Sex : In the early weeks, the embryo has two sets of ducts, viz, i. Mullerian duct and ii. Wolffian duct systems.

If on and from 8th week, the embryo does not get exposure to the effects of the embryonic testis i.e. if the fetal testes do not start to develop, as in XX genotype, the Mullerian system survives and the Wolffian ducts degenerate. On the other hand, if the embryo begins to be exposed to the effects of its own testes, on and from 8th week, the Wolffian system develops and the Mullerian ducts degenerate.

From the Wolffian ducts, the male accessory sex organs develop. From the Mullerian ducts the female accessory sex organs grow.

This means, that the natural tendency for the fetus is to develop female phenotype. Only when the testes are present, the accessory sex organs develop to form penis, prostate, seminal vesicles ctc. Thus, If in a genotype XY, the testis be removed around 7th week of intrauterine life, the new born will have fallopian tube, uterus, vagina and vulva, although its genotype will remain XY.

Mechanism of action of testis :

1. The embryonic testis produces a polypeptide hormone called, Mullerian duct inhibiting factor, which causes degeneration of the Mullerian duct.

2. On and from the 8th week, the embryonic testis begins to produce testosterone which directly causes development of the following structures.
   a. Seminal vesicle
   b. Vas deference
   c. Epididymis.

In some other structures of the accessory sex organs, testosterone is converted into dihydrotestosterons by an enzyme called 5th reductase. It is the dihydrotestosterone (and not the testosterone) that causes development of the rest of the accessory male sex organs, like : a. prostate, and b. penis. Therefore, testosterone ultimately speaking (i.e, directly or via dihydrotestosterone) causes development of all accessory male sex organs.

Although these growths start in embryonic life, they (i.e, the growth) again reappear with a gusto in the pubertal period. Some males have smaller size penis, while others have big size penis. It is possible that the smallness or bigness of the size of the penis due to the presence of too few or too many receptors for dihydrotestosterone and is no index of the sexual virility.

Brain and the sex differentiation : There are some anatomical and functional differences in between males and females in certain areas of the brain. Thus, in the embryonic life, when the fetal hypothalamus receives exposure to androgen (from its own testes) that is, in male fetus, it undergoes some changes due to which two important changes (in function) occur as follows :

i. When today's fetus becomes post pubertal boy, the pituitary gonadotropins are secreted constantly. Absence of androgenic exposure of the fetal hypothalamus causes it (i.e. the hypothalamus) to stimulate the anterior pituitary in a cyclic way. Therefore, in females, pituitary gonadotropins are secreted cyclically, so ovarian cyale and the menstrual cycles occur cyclically.

ii. If androgenic exposure occurs, on attaining post pubertal stage, the subject develops an attraction for females.

Some histological changes also occur (as a result of androgenic exposure of the fetal hypothalamus). These include some changes of the organelles within the cells of the hypothalamus.

Primary sex organ

It may be defined as the sex gland which are responsible for gametogenesis & controls the development & activity of accessory sex organ.

i. In male : Testes .
ii. In Female : Ovary.

Function of primary sex organ

1. Exocrine : Production of gamates (gamato genesis)
2. Endocrine : Production of hormone.
3. Controls the develop ment and activity of accessory sex organs.

Sex hormones

Sex hormones exert effects on reproductive function. In both sexes, the gonads secretes sex hormones.

i. *Androgens* are the steroid sex hormones that are masculinizing in their action.
ii. *Testosterone :* Secreted from testes.
ii. *Estrogens* are those that are feminizing. The ovaries secrete large amounts of estrogens.
iii. *Progesterone* : Secreted from ovaries, a steroid that has special functions in preparing the uterus for pregnancy.
iv. *Relaxin :* A polypeptide hormone, secreted from ovaries particularly during pregnancy, which loosens the ligaments of the pubic symphysis and softens the cervix, facilitating delivery of the fetus.
v. *Inhibin B* : A polypeptide that inhibits FSH secretion in both sexes.
vi. Aterior pituitary gonadotropins, FSH, and LH : The secretory and gametogenic functions of the gonads are both dependent upon them.

In males, gonadotropin secretion is noncyclic; but in postpubertal females an orderly, sequential secretion of gonadotropins is necessary for the occurrence of menstruation, pregnancy, and lactation.

(Q. 00. Name the sex hormones?) *(Ref. Ganong 22th Edition; P-411)*

Q. 00. **What are the gonadotropin? Where are they formed? Discuss their function & regulation of secretion.**

Ans.

i. Gonadotropins are gonad stimulaing hormones. They are FSH, and LH.
ii. *Secreted from* :
   a. FSH, and LH : anterior pituitary.
   b. Human chorionic gonadotropin : Placenta.
iii. *Function* : The secretory and gametogenic functions of the gonads are both dependent upon gonadotropin.
iv. *Regulation of secretion :* The sex hormone and inhibin B feed back to inhibit gonadotropin secretion.
   a. In males : gonadotropin secretion is noncyclic.
   b. *In postpubertal females* : an orderly, sequential secretion of gonadotropins is necessary for the occurrence of menstruation, pregnancy, and lactation.

(Q. Name the gonadotropins) *(Ref. Ganong 21th Edition; page-415)*

Inhibin

The hormone inhibin is a glycoprotein, like both LH and FSH, having a molecular weight between 10,000 and 30,000.

Source and function :

a. *Sertoli cells of testis* : Inhibin has a strong direct effect on the anterior pituitary gland in inhibiting the secretion of FSH

and possibly a slight effect on the hypothalamus in inhibiting secretion of GnRH.

Its potent inhibitory feedback effect on the anterior pituitary gland provides an important *negative feedback mechanism for control of spermatogenesis*, operating sirnultaneously with and in parallel to the negative feedback mechanism for *control of testosterone secretion.*

(Ref. Guyton & Hall-11th Edition; page 1007)

ii. *Luteal cells* : Secrete small amounts of the hormone inhibin. Inhibin inhibits secretion by the anterior pituitary gland, especially FSH secretion. As a result, both FSH and LH in the blood fall to low concentrations, and loss of these hormones finally causes the corpus luteum to degenerate completely, a process called *involution of the corpus luteum.*

Final involution normally occurs at the end of almost exactly 12 days of corpus luteum life, which is around the 26th day of the normal female sexual cycle, 2 days before menstruation begins. At this time, sudden cessation of secretion of estrogen, progesterone, and inhibin by the corpus luteum removes the feedback inhibition of the anterior pituitary gland, allowing it again to begin secreting increasing amounts of FSH and LH. The FSH and LH initiate growth of new follicles, to begin a new ovarian cycle. And the paucity of secretion of progesterone and estrogen at this time also leads to menstruation by the uterus.

(Ref. Guyton & Hall-11th Edition; page 1015)

Puberty

i. *Definition* : The onset of reproductive life is called puberty. It is the time when the endocrine and gametogenic functions of the gonads have first developed to the point where reproduction is possible.

ii. *Age of onset* : It occurs about two year earlier in female.
   a. In girls, it starts in 8-13 yrs.
   b. In boys, it starts in 9-14 yrs.

(Ref. Ganong 22th edition; page 418)

iii. *Factors influce the onset of puberty* : The onset of puberty is greatly influenced by :
   a. Heriditary factor
   b. Environmental factor
   c. Nutritional status
   d. Hormonal factor.

iv. *Probable mechenisms initiating puberty are* :
   a. Withdrawl of central inhibition of GnRH release.
   b. Release of sufficient amounts of pituitary gonadotropins under the influence of hypothalamic GnRH.

v. *Gross changes at puberty* :
   a. Enlargement of testes and genitalia (boys).
   b. Breast bud enlargement ii girls.
   c. Pubic and axillary hair growth.
   d. Begining of meanstruation i.e mnarche in girls.
   e. Change of voice etc.

Precocious puberty

i. Definition : Development of menarche (girls) or secondary sex characteristics (boys) before the age of 9 years is premature, and called precocious puberty.

ii. *Characteristics* :
   a. Premature breast and pubic hair development
   b. Puberty starts too early, but otherwise normal pubertal pattern (gametogenesis is possible).

iii. Cause :
   a. Most frequently caused by hypothalamic disease i.e. withdrawal of inhibition of GnRH release.

Precocious pseudopuberty

Early development of secondary sexual characteristics without gametogenesis due to abnormal exposure of immature male to androgen, or females to estrogen is called precocious puberty.

Delayed puberty

Failure of testicular development by the age of 20 or menarche has fail to occur by the age of 17 is termed as delayed puberty.

Some important terms :

i. ***Thelarche*** : the devdlopment of bresat.

ii. ***Pubarche*** : The development of axillary and pubic hair.

iii. ***Menarche*** : The first menstrual peroid.

iv. ***Adrenarche*** : An increase in the secretion of adrenal androgens at the time of puberty.

(Ref. Ganong 22th Edition; page 419)

Clinical

Klinefelter's syndrome

Klinefelter's syndrome is the most common sex *chromosomal disorder*. The people have genitalia of normal male.

i. *Incidence* : 1 in 1000 males.

ii. *Characteristics* :
   a. *Karyotype* : 47 XXY
      Total 47 chromosome instead of the normal 46; extra chromosome is X chromosome.
   b. *Phenotype* : Male often with gynaecomastia i.e. enlargement of male breast.

iii. *Features* :
   a. Gonads : Small testes
   b. Poorly developed secondary sexual charac- teristics
   c. Infertility
   d. Mental retardation.

Turner's syndrome.

Turner's syndrome is a sex chromosome monosomy *(chromosomal disorder)* in which indivi duals have an X

chromosome only and no second X or Y chromosome.

i. *Incidence* : It occurs in 1 in 2500 females.

ii. *Characteristics* :
   a. *Karyotype* : 45 XO
      Total 45 chromosome instead of the normal 46; deficit of a X or Y chromosome.
   b. *Gonads* : rudimentary or absent
   c. *Phenotype* : female.

iii. *Features* :
   a. The affected person develops female external genitalia
   b. Short stature
   c. Webbed neck
   d. Increase carrying angle
   e. Loss of secondary sexual characteristics
   f. Primary ammenorrhoea
   d. Coarctation of aorta.

Trisomy X *(triple X syndrome).*

Trisomy X is a sex chromosomal disorder.

i. *Incidence* : occurs 1 in 12000 females.

ii. *Characteristics* :
   a. Karyotype : 47 XXX
      Total 47 chromosome instead of the normal 46; 1 extra X chromosome.
   b. Phenotype : female
   c. Usually asymptomatic; but in 20% cases mild mental retardation.

Double Y syndrome.

Double Y syndrome is a sex chromosomal disorder.

i. *Incidence* : Occurs in 1 in 800 males.

ii. *Characteristics* :
   a. Karyotype : 45 XYY
      Total 47 chromosome instead of the normal 46; excess of a Y chromosome.
   b. Phenotype : male

iii. *Features include* :
   a. Tall stature
   b. Fertile
   c. Minor mental and psychiatric illness
   d. High incidence of criminal activities.

Down's syndrome *(Trisomy 21)*

Down syndrome is the most common *autosomal disorder*. Cells bear extra copy of chromosome because of nondisjunction either in the first or second meiotic division- hence called *trisomy 21.*

i. *Incidence* : occurs 1 in 700 live births.

ii. *Characteristics* :
   a. Karyotype : 47 + 21
      Total 47 chromosomc instead of the normal 46; there is an extra chromosome 21.

iii. *Features* :
   a. Flat facies
   b. Slanting eyes
   c. Low set ears
   d. Epicanthic fold
   e. Simian crease (single palmer crease)
   f. Short stubby tingers
   g. Hypotonia
   h. Variable mental retardation
   i. IQ less than 50
   j. Congenital heart disease
   k. Love music.

True hermaphroditism.

Nondisjunction may occur during the early mitotic divisions after fertilization- which results in the production of *mosaic* (patient with two different cell lines with different chromosome complements).

True hermaphroditism is the condition in which an individual have both the testes and ovaries and is probably due to XX/XY mosaicism.

i. *Characteristics* :
   a. Karyotype : 46 XX/XY mosaic
   b. Phenotype : Male or ambiguous
   c. Gonads : Testes and ovaries.

Q. 00. **What are the hormonal abnormalities in sexual differentiation?**

Ans. Abnormalities in the action of androgens, Mullerian regression factor (MRF), and testosterone during developmental period may cause following disorders :

i. Female hermaphroditism
ii. Male hermaphroditism
iii. Testicular feminizing syndrome.

A pseudoherrmaphrodite is an individual with the genetic constitution and gonads of one sex and the genitalia of the other sex.

Female hermaphroditism : Development of male external genitalia in genetic female is called female hermaphroditism.

1. *Characteristics* :
   a. Karyotype : 46 XX (i.e. genetic female)
   b. Phenotype : Female with male external genitalia.
   b. Gonads : ovary.
2. *Cause* : Genetic female exposed to androgens during the 8^{th} - 13^{th} weeks of gestation

Male hermaphroditism : Development of female external genitalia in genetic male is called male hermaphroditism.

1. *Characteristics* :
   a. Karyotype : 46 XY (i.e. genetic male)
   b. Phenotype : Male with female external genitalia.

c. Gonads : Testes.

2. *Causes* :
   a. Androgen resistance
   b. Defective embryonic testes.

Testicular feminizing syndrome : It is a condition due to defective androgen receptor in which rhe external genitalia are female, but the vagina ends blindly because there are no female internal genitalia.

Important criteria are :

a. Karyotype : 46 XY
b. Phenotype : Ambiguous or infantile female
c. Gonads : Testes
d. Features :
   - Breast enlargement at puberty
   - No menstruation.

Male Reproductive System

Male Sex Organs

A. *Primary sex organ :* Testes

Functions : Testis acts as a mixed gland. It performs both exocrine and endocrine functions.

i. Exocrine : Spermatogenesis (Production of spermatozoa.
ii. Endocrine : Production of Testosterone.

B. *Accessory sex organs :*

1. Penis with Scrotum.
2. Prostate.
3. Seminal vesicle.
4. Urethra.
5. Epididymis.
6. Vas deference.
7. Ejaculatory duct.
8. Bulbo-urethral gland.

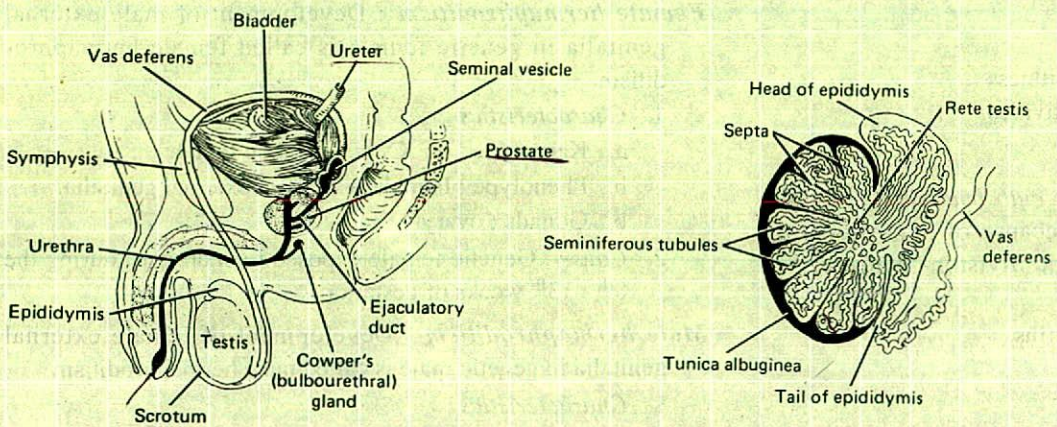


Fig. 9 -2. *Left : Male Reproductine System; Right : Duct system of the testis.*

Testes

Structure of testes : The testes are made up of loops of Seminiferous tubules, in the walls of which the spermatozoa are formed from the primitive germ cells (Spermato -genesis). Both ends of each loop drain into a network of ducts in the head of the epididymis. From there Spermatozoa pass through the tail of the epididymics into the vas deferens. They enter through the ejaculatory ducts into the urethra in the body of the prostate at the time of ejaculation.

Between the tubules in the testes are nests of cells containing lipid granules, the interstitial cells of Leyding which secrets testosterone into the blood stream.

The spermatic arteries to the testes are tortous, and blood in them runs porallel but in the opposite direction to blood in the pampiniform plexus of spermatic veins. This anatomic arrangement may persist countercurrent exchange of heat and testosterone.

Blood Testes Barrier

The walls of the seminiferous tubules are lined by primitive germ cells and by sertoli cells -large, complex glycogen-containing cells that stretch from the basal lamina of the tubule to the lumen. Tight junction between adjacent sertoli cells near the basal lamina form a *blood-testis barrier* that prevents many large molecules from passing from the interstitial tissue and the part of the tubule near the basal lamina (basal compartment) to the resion near the tubular lumen (adluminal corpartment) and the lumen. How ever steroids penetrate this barrier with ease and there is evidence that some proteins pass from the sertoli cells to the leyding cells and vice versa in a paracricu fashion. In addtion, maturing germ cells must pass through the barrier as they move to the lumen. This appears to occur without disruption of the barrier by progressive break down of the tight junctions above the germ cells, with concomitant formatrom of new tight junction below them.

The fluid in the lumen of the seminiferous tubules is quite different from plasma; it contains very little protein and glucose but is reach in androgens, estrogens, K^+, inositol, and glutamic and aspartic acids. Maintenance of its composition presumably depends on the blood testes-barrier. The barrier also protects the germ cells from blood-born noxious agents, prevents antigenic products of germ cell division and maturation from entering the circulation and generating an

autoimmune response, and may help establish an osmotic gradient that fascilitates movement of fluid into the tubular lumen.

Secondary sexual characteristic of male

1. *External genitalia* : Penis increase in length and width, scrotum become pigmented and rugose.
2. *Internal genitalia* : Seminal vesicles enlarge and secrete and begin to form fructose. Prostate & bulbourethral gland enlarge and secrete.
3. *Voice* : Larynx enlarges; vocal cord increase in length and thickness, and voice becomes deeper.
4. *Hair growth :*
   i. Beard appears. Hair line on scalp recedes anterolaterally.
   ii. Pubic hair grows with male (triangle with apex up) pattern.
   iii. Hair appears in axilla, on chest and arround the anus. Genera body hair increase.
5. *Mental changes* : *More agressive, active attitude,* interest in opposite sexdevelops.
6. *Body conformation* : Shoulder broden, muscle enlarge.
7. *Skin* : Sebaceous gland secretion thickens and increases (predisposing to acne).

(Ref. Ganong 22th edition, Page-430).

Male Hormonal system

Male hormonal system consists of three hierarchies of hormones as follows :

1. Hypothalamic hormone :
   a. Gonadotropin-releasing hormone (Gn RH), Previously also called luteinizing hormone releasing hormone.
2. Anterior pituitary hormones :
   a. Luteinizing hormone (LH) : Luteinizing hormone is the primary stimulus for the secretion of testosterone by the testes.
   b. Follicle stimulating hormone (FSH) : FSH mainly stimulates spermatogenesis.
3. Hormones of the testes :
   a. Testosterone (Secrects from interstitial cells of leyding)
   b. Inhibin (Secrects from the sertoli cells)

Reproductive function of male

1. Spermatogenesis, which means simply the formation of sperm.
2. Performance of the male sexual act.
3. Regulation of male reproductive functions by the various hormones.

(Ref. Guyton & Hall-11th edition; page 996)

Function of male reproductive hormones

1. Spermatogenesis, which means simply the formation of sperm.
2. Performance of the male sexual act.
3. Regulation of male reproductive functions by the various hormones.

Associated with these reproductive functions are the effects of the male sex hormones on the accessory sexual organs, cellular metabolism, growth, and other functions of the body.

(Ref. Guyton & Hall-11th edition; page 996)

Spermatozoa

Spermatozoa consists of-

i. Head
ii. Neck
iii. Body
iv. Tail.

Head : Oval in shape. The head is a condensed nucleus about 40 % DNA and rich in arginine. The nucleus is covered in its anterior-twothird by acrosome. The acrosome is formed by golgi apparatus and can liberate a chemical substance, hialuronic acid which enables the sperm to pierce the zona pellucida of ovum.

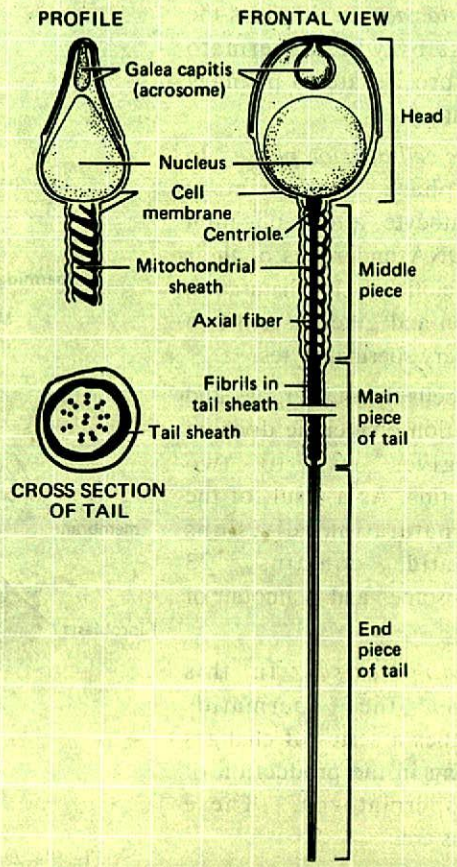


Fig. 9-3. *Structure of the human spermatozoan.*

Neck : Short, connecting the head with body. In the neck the axial filaments consist of three bundles of fibrils which connect the three basal granules.

Body : It is cylindrical in form and is the engine room of spermatozoon. In which cisternae mitrocondrialis are found.

Tail : It has three major component -

a. A central skeleton constructed of 11 microtubules, collec- tively called axoneme.
b. A thin cell membrane covering the axoneme.
c. A collection of mitrochondria surrounding the axoneme.

Gametogenesis

Gametogenesis is the process in which both male and female germ cells undergoes a number of chromosomal and morphological changes in the preparation for fertilization.

(Ref. Lang Man 5th Page 16)

Spermatogenesis

Spermatogenesis is the maturation process from primitive germ cell to mature gamate in male.

(Ref. Lang Man 5th Page 17)

Stages of spermatogenesis : Spermatogenesis has three different stages :

i. *Spermatocytogenesis :* It is the process by which spermato gonia proliferate to primary spermatocyte.

ii. *Meiosis cell division phase :* In this phase the primary spermatocyte, after replication their DNA undergoes of their first meiotic or, 1st maturation division and gives rise to two secondary spermatocytes.

These cells then undergoes 2nd maturation or meiotic division and gives rise to two spermatids. As a result of the two maturation divisions spermatid contains 23 chromosomes and n amount of DNA.

iii. *Spermiogenesis :* In this process the spermatids undergoes a series of changes resulting in the production of the spermatozoa. These changes are :

a. Formation of acrosome.
b. Condensation of nucleus.
c. Formation of neck, middle piece & tail.
d. Sheding of most of the cytoplasm.

(Ref. Lang Man 5th page 14-15)

Hormonal regulation of spermatogenesis :

1. *Testosterone :* Secreted by the Leyding cells located in the interstitium of testis, is essential for growth and division of germinal cells in forming sperm.
2. *Lutenizing hormone (LH) :* Secreted by anterior pituitary gland and stimulate the Leydig cell to secrete testosterone.
3. *Follicle stimulating hormone (FSH) :* Secreted by the anterior pituitary gland, stimu-late the sertoli cells and without this stimulation the conversion of the spermatids to sperm (the process of spermiogenesis) will not occur.
4. *Growth hormone :* Growth hormone specifically promotes the early division of spermatogonia and also maintain the metabolic function of testis.
5. *Estrogen :* Formed from testosterone by the Sertoli cells when they are stimulated by FSH, are probably essential for conversion of the spermatids to sperm (Process of spermioenesis) and helps in maturation of sperm.

(Ref. Guyton & Hall-11th edition; page 998)

Diagramatic representation of spermatogenesis : Spermato-

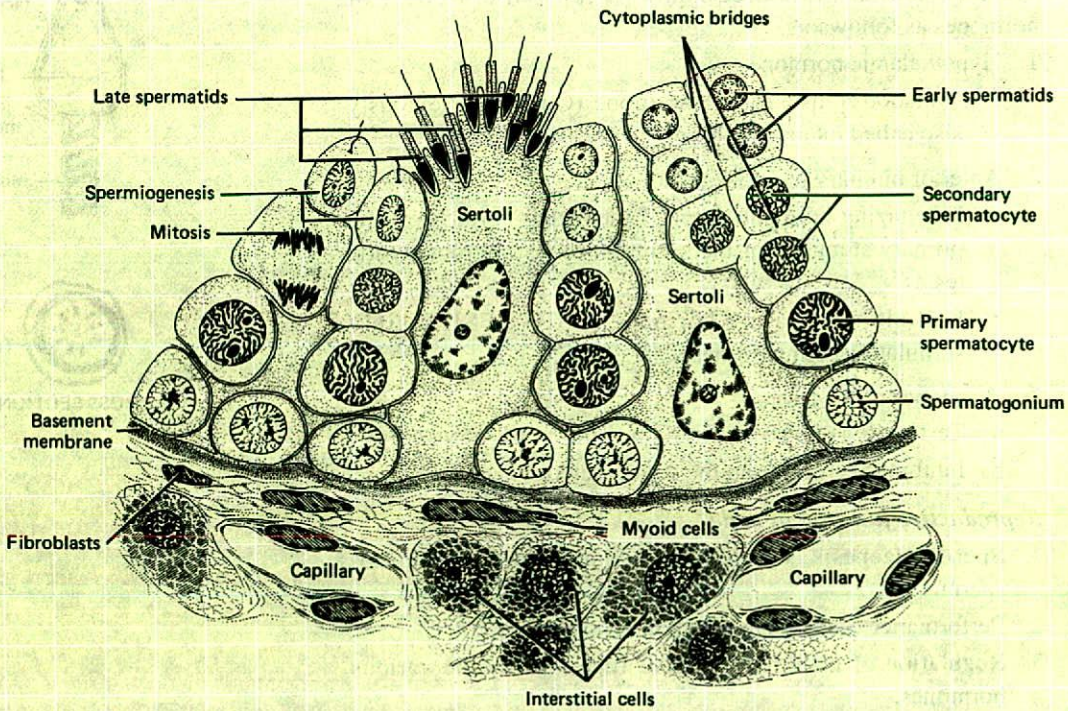


Fig. 9-4. *Diagramatic representation of spermatogenesis. Seminiferous epithelium-- mature germ cells remain connected by cytoplsmic brodges through the early spermatid stage and that these cells are closely invested by Sertoli cell cytoplasm as they move from the basal lamina to the lumen.*

gonia → Primary spermatocyte → 2ndary spermatocyte → Spermatid → Spermatozoa.

Diagramatic regulation of spermatogenesis

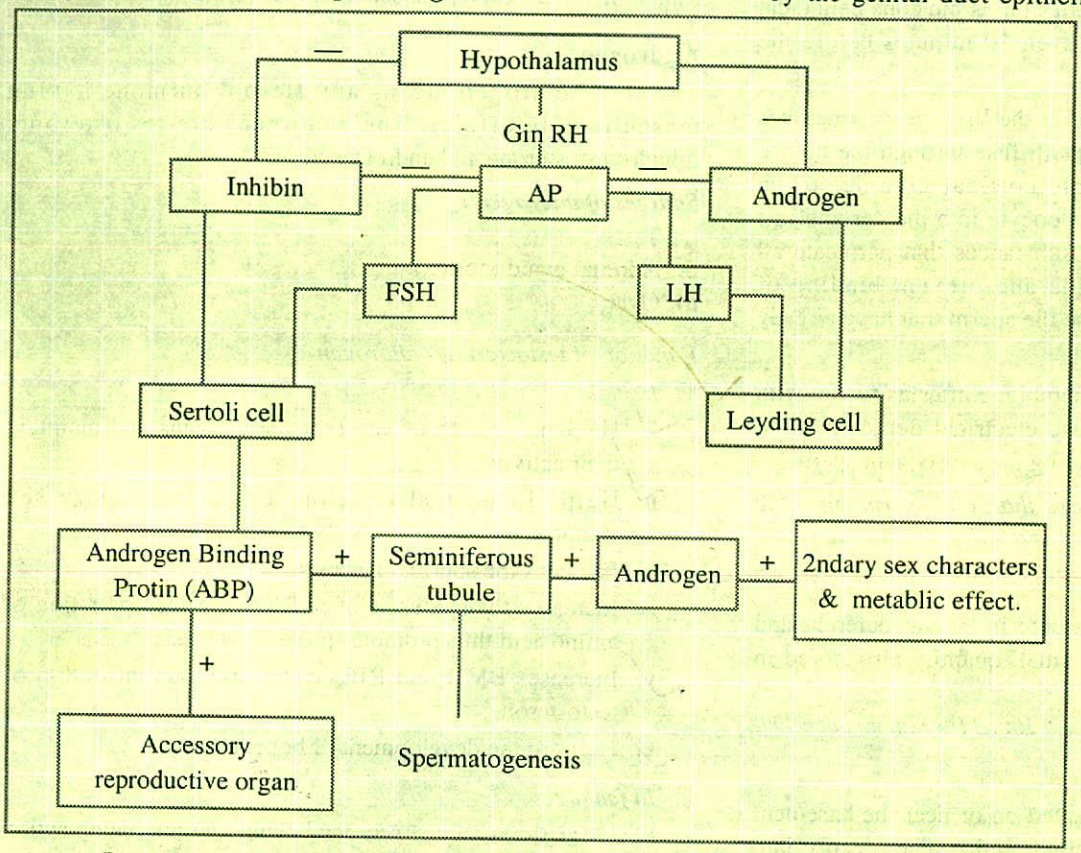


Fig : 9-4. *Digramatic Regulation of spermatogenesis.* *(Ref. Selkert 5th page 648)*

Maturation of sperm (in the epididymis) :

It is the process by which newly formed non-motile young un-fertile sperm become motile and get the capacity for fertilization.

Following formation in the seminiferous tubules, the sperm require several days to pass through the 6-meter-long tubule of epididymis. Sperm removed from the seminiferous tubules and from the early portion of the epididymis are completely non-motile and they can not fertilize the ovum. However, after the sperm have been in the epididymis for some 18 to 24 hours also become capable of fertilizing the ovum; if placed in the uterus.

The Sertoli cells and the epithelium of the epididymis secret a special nutrient fluid containing hormones (both testosterone and oestrogen), enzymes and special nutrients that may be important or even essential for sperm maturation.

(Ref. Guyton & Hall-11th edition; page 999)

Capacitation of sperma tozoa

It is the process by which the sperm develop capability to penitrate the granulosa cell that cover the ovum after deposited into the female genital tract.

Mechanism of capacitation : Although the sperma tozoa are said to be "mature" when they leave the epididymis, their activity is held in check by multiple inhibitory factors secre ted by the genital duct epithelia. Therefore, when they are first expelled in the semen, they are unable to perform their duties in fertilizing the ovum. However, on coming in contact with the fluids of the female genital tract, multiple changes occur that activate the sperm for the final processes of fertilization. These collective changes are called capacitation of the spermatozoa. This normally requires from 1 to 10 hours. Some changes that are believed to occur are the following.

1. The uterine and fallopian tube fluids away the various inhibitory factors that had suppressed sperm activity in the male genital ducts.
2. While the spermatozoa remained in the fluid of the male genital ducts, they were continually exposed to many floating vesicles from the seminiferous tubules containing large amounts of cholesterol. This cholesterol was continually donated to the cellular membrane covering the sperm acrosome, toughening this membrane and preventing release of its enzymes. After ejacu- lation, the sperm that are deposited in the vagina swim away from the cholesterol vesicles upward into the uterine fluid, and they gradually lose much of their excess cholesterol over the next few hours. In so doing, the membrane at the head of the sperm becomes much weaker.
3. The membrane of the sperm head also becomes much more permeable to calcium ions, so that calcium now enters the sperm in abundance and changes the activity of the flagellum, giving it a powerful whiplash motion in contrast to its previously weak undulating motion. In addition, the calcium ions probably cause changes in the intracellular membrane that covers the leading edge of the acrosome, making it possible for the acrosome to release its enzymes rapidly and easily as the sperm penetrates the granulosa cell mass surrounding the ovum and even more so as it attempts to penetrate the zona pellucida of the ovum itself.

Thus, multiple changes occur during capacitation. Without them, the sperm cannot make its way to the interior of the ovum to cause fertilization. *(Ref. Guyton & Hall-11th ed, page 1000)*

Q. **Why does only one sperm enter the oocyte?**

Ans. The reason is not entirely known, but some of the facts are the following.

1. *First,* only a few sperm ever get as far as the zona pellucida, so that it might be 10, 20 or even 30 minutes before the second sperm arrives.
2. *Second,* within a few minutes after the first sperm penetrates the zona pellucida, calcium ions diffuse through the oocyte membrane and cause multiple cortical granules to be released by exocytosis from the oocyte into the perivitelline space. These granules contain substances that permeate all portions of the zona pellucida and prevent binding of additional sperm and even cause the sperm that have already bound to fall off.
3. *Third,* changes in the oocyte membrane after its fusion with the sperm are believed to cause electrical depolarization; this, too, may play a role in fending off subsequent sperm.

At any *rate, almost never does more than one sperm enter the oocyte during fertilization.*

Storage of sperm

Following maturation sperms are stored in the vas deferens and the ampulla of vas deferens but a small quantity also stored in the epididymis.

(Ref. Guyton & Hall-11th edition; page 999)

Sertoli cells

Are quite few in numbers and situated on or near the basement membrane of the seminiferous tubule and project deeply into the lumen. They are also known as sustentacular cells, nurse cells, foot cells or branched cells. These cells have a large vesicular nucleus with a characteristic nucleus. The cells contain quite large amount of glycogen. The membranes of the sertoli cells are tightly adherent to each other at their bases, forming a barrier, called *blood-testis barrier.*

Function of cells of Sertoli :

1. It provide appropriate nutrients for the developing and newly formed sperm.
2. It provide a special fluid environment in which germinal cell develops.
3. It helps in convertion of spermatid to sperm (the process of spermiation).
4. Sertoli cell secretes-
   i. Mullerian inhibitory factor
   ii. Estradiol
   iii. Inhibin.

(Ref. Guyton & Hall-11th edition)

Interstitial cells of Leyding : The Leydig cells lie in the interstices between the seminiferous tubules and constitute about 20% of the mass of the adult testes. Leydig cells are almost non-existent during childhood, but they are numerous in the newborn male infant and also in the adult male after puberty.

Function : They secret testosterone.

Androgen

The term androgen means any steroid hormone having masculinizing effects. The andorgens are-testosterone, dihydrotestosterone and androstenedione.

Sources of androgen :

i. Testis
ii. Adrenal gland (cortex).
iii. Ovary

Function of testosterone (androgen)

1. *In male :*
   i. Helps in growth of accessory sex organs and maintain their activity.
   ii. Helps in normal development of secondary sex characters.
   iii. Facilates the spermatogenesis.
   iv. Increases the synthesis of m RNA and incorpo ration of amino acid thus promotes protein synthesis.
   v. Increases BMR and RBC count after administration of testosterone.
   vi. Helps in the development of bone, muscle.
2. *In female :*
   i. Large doses of testosterone having masculi nizing action like enlargement of clitoris, and growth of hair on the face.
   ii. Inhibit the pituitary function as in male.
3. *In male foetus :*
   i. It is responsible for the sex determination and development of male external genitalia.
   ii. Helps in the descent of testes during foetal life.

Semen

It is the fluid, which is ejaculated during male sextual act is composed of the fluids from the vasdeference, prostate, seminal vesicle and from the mucous gland, especialy bulbourethral gland.

Characteristic of semen :

Colour	:	White, opalescent.
Specific gravity	:	1.028
PH	:	7.35 -7.50
Amount	:	2-4 ml/ejaculation.
Sperm count	:	Average 100 million/ml, with fewer than 20% abnormal forms.

Composition of semen :

I. Sperm : Average 100 million/ml, with fewer than 20% abnormal forms.

II. *Other components* :

i. From seminalvesicle contribute 60% of total volume
   a. Fructose (1.5-6.5 mg/ml)
   b. Phosphorylcholine
   c. Ergothioneine
   d. Ascorbic acid
   f. Flavins.
   g. Prostaglandins

ii. From prostate (Contribute 20%of total volume)
   a. Spermine
   b. Citric acid
   c. Cholesterol, phospholipids
   d. Fibrinolysin, fibrinogenase,
   e. Zinc
   f. Acid phosphatase
   g. Phosphate (PO_4^{-3})
   h. Bicarbonate (HCO_3^-) Buffer
   i. Hyaluronidase.

***Speed** : Human sperms move at a speed of about 3 mm/minute through the female genital tract. Sperms reach the uterine tubes 30-60 minutes after copulation.*

(Ref. Ganong 22th edition, Page 427)

Effect of sperm count on fertility : The usual quantity of semen ejaculated during each coitus averages about 3.5 milliters, and in each milliliter of semen is an average of about 120 million sperm, although even in normal males this can vary from 35 to 200 million. This means an average total of 400 million sperm are usually present in the several milliliters of each ejaculate. When the number of sperm in each milliliters falls below about 20 million, the person is likely to be infertile.

Thus even though only a single sperm is necessary to fertilize the ovum, for reasons not understood, the ejaculate usually must contain a tremendous number of sperm for only one sperm to fertilize the ovum.

(Ref. Guyton & Hall-11th edition; page 1001)

Prostatic fluid

The Prostate gland secreates a thin, milky, alkaline fluid which increases the volume of semen.

i. *Composition of prostatic fluid :* Citrateion, Calcium ion, Acid phosphate ion, a clotting enzyme, a profibrinolysin.

ii. *Function of prostatic fluid :*
   1. It adds the bulk of semen.
   2. Its alkalinity neutralizes the acidity of the vaginal fluid (P^H 3.5 to 4.0) and the fluid of vas deference enhances the motility and fertility of the sperm.

(Ref. Guyton & Hall-11th edition; page 999)

Seminal fluid

Seminal vesicles secrete a mucoid materials which increases the volume of semen.

i. *Composition of seminal fluid :* An abundance of fructose and other nutrient substance as well as large quantities of prostaglandin & fibrinogen.

ii. *Function of seminal fluid :*
   a. It adds greatly the bulk of semen about 60%.
   b. Fructoes and other nutrients provide nutrient to the ejaculated sperm until one of them fertilizes the ovum.
   c. Prostagladins aid fertilization by :
      1. Reacting with cervical mucus to make it more receptive to spermmovement.
      2. Causing reverse peristaltic contraction in the uterus and fallopian tubes to move the sperm toward the ovaries.

(Ref. Guyton & Hall-11th edition; page 999)

Sterility

Sterility means loss of reproductive capacity.

Cause of sterility :

i. Failure of erection of penis
ii. Failure to discharge sufficient quantity of semen
iii. Less sperm count (below 60 million in per ejaculation)
iv. Presence of more than 20% abnormal sperm in semen.
v. Impairment movement of sperm due to-
   a. Genital infection
   b. Malnutrition
   c. Acidic P^H
vi. Absence of hyaluronidase in the head acrosome.

Impotancy

Inability to perform sexual intercourse i,e. failure to erection of penis.

Cause of impotancy :

i. Malnutrition
ii. Mental unability
iii. Genital infection
iv. Excessive utilization.

Castration

Removal of testis is known as castration.

Effect of castration : The effects are variable in different subjects. Some effects are more pronounced than others. These changes are :

i. Seminal vesicle and prostate atrophy as its development and maintenance depend on the secretion of testosterone which is lacking.
ii. Loss of sexual desire and activities in most subject, those these persist in few.

iii. Falliny of hair occurs along with the tendency to baldness sparseness of beard and moustache and recession of convex hair margins of the pubis.
iv. Sometimes femine deposition of fat occurs.
v. No change in the size of penis.
vi. No change in the voice.
vii. Psychological upset in conveniences the subject greatly.

Eunuchism

It is a condition when a boy loses his testes prior to puberty. In which he continues to have infantile sexual characteristics through out life. The height of the adult eunuch is slightly greater than that of the adult man, although the bones are quite thin, the muscles are considerably weaker than normal man, the sexual organs and secondary sexual characterstics remain those of a child. The voice is child like, there is no loss of hair on head and the normal musculine hair distribution on the face and else where does not occur.

(Ref. Guyton & Hall-11th edition)

Adiposogenital syndrom

It is a condition in which severe obesity develops along with eunuchism. It is also called *Frohlich's syndrom* or *hypothalamic eunuchism.*

Damage of certain areas of the hypothalamus greatly decreases gonadotropic hormone secretion and stimulates feeding center, causing the person to greatly overeat. Consequently the person develops severe obesity along with enuchism. This phenomenon is called adiposogenital or Frohlich's syndrom.

(Ref. Guyton & Hall-11th edition)

Chryptorchidism

It means failure of a testis to descend from the abdomen into the scrotum. During late stages of gestation (about 3 weeks to 1 month before the birth of the baby) the testes descend from abdomen through the inguinal canal into the scrotum. Occasionally this descent does not occur at all or occurs incompletely, So that one or both testes remain in the abdomen, in the inguinal canal or elsewhere along the route of descent.

Condtion of chrytorchidism : In chryptorchidism, the testicle is incapable of forming sperm. Few degree higher temperature in the abdomen than the scrotum is enough to cause degeneration of the tubuler epithelium and consequently to cause sterility.

(Ref. Guyton & Hall-11th edition)

Male Sexual Act

Sources of male sexual stimulation : These are areas or events from where sexual stimulation arises :

1. Glans penis .
2. Adjacent to penis.
3. Anal epithelium, the scrotum and perineal structures etc.
4. Internal structures such as- Urethra, the bladder, prostate, seminal vesicles, testes and the vas deferens, when irritated.
5. Filling of the sexual organ with secretion.
6. Infection and inflammation of the sexual organs.
7. 'Aphrodisiac' drugs- comtharides etc.
8. Psychic elements- Sexual thinking or dreaming, visual stimuli etc.

(Ref. Guyton & Hall-11th edition; page 1001)

Stages of male sexual act : It is divided into following stages :

a. Erection
b. Lubrication
c. Emission & Ejaculation.

Erection : Erection is the 1st effect of male sexual act and the degree of erection is directly proportional to stimulation. It is a vascular phenomenon and is controlled by parasympathetic (S 2, 3, 4) With sufficient stimulation the helicine arteries dilates and engorment of the sinuses of the penis along with venous retardation also occcur.

Lubrication : During sexual stimulation the para sympathetic impulses, cause the bulbourethral and urathral glands to secrete mucous which lubricates female genitalia during copulations.

Emission & ejacualtion :

a. *Emission :* It is the process of secretion of semen into the urethra.
b. *Ejaculation proper :* It is the process of propulsion of semen out of the urethra by the contraction of urogenital muscles.

Emission and ejaculation are the culmination of male sexual act. When the sexual stimulus are extrimely intense, the sympathetic impulse (L_1 & L_2) pass to the genital organ to initiate emission and ejaculation.

(Ref. Guyton & Hall-11th edition; page 1002)

Clinical

Teratoma : Tumors of the germinal epithelial cell. Germinal cells are capable of differentiating in to many type of cell and so this tumour contain multiple tissues, such as placental tissue, hair, teeth, bone, skin and so forth.

(Ref. Guyton & Hall-11th edition; page 1009)

Gynaecomatia : Over growth of male breast is called Gynaecomatia. *Cause :* When teratoma in male contain significant amount of placental tissue, the tumour may secrete large quantities of chorionic gonodrtropin hormone and also oestrogen, which then cause overgrowth of breast.

(Ref. Guyton & Hall-11th edition; page 1009)

Clitmacteric : The decrease in male sexual function is called male climetric.

Symptoms : Occasionally it is associated with symptoms of

a. Hot flashes
b. Suffocation

c. Psychic disorders etc.

Characteristics :

a. Progressive loss in sexual function with reduction in morning erections and frequency of intercourse.
b. Testicular volume diminished
c. FSH and LH levels gradually rise.

(Ref. Guyton & Hall-11th edition; page 1008)

Q. Why spermatogenesis does not occurs before puberty?

Ans. Because before puberty hypothalamus remains dormant and does not secrete leutinizing hormone releasing factor (LHRF).

So, that anterior pituitary cannot secret LH and Leydig cell can not stimulated for secretion of androgen, as a result seminiferous tubule can not produce spermatogonia.

(Ref. Guyton & Hall-11th edition)

Effects of removal of testes before puberty

The following changes take place and all of are due to lack of testicular hormone :

i. Lack of development of accessory organs of reproduction e.g, penis, scrotum, seminal vesicle and prostate do not grow and remain infantile.
ii. Complete failure of reproductive cycle and permanet sterility.
iii. Lack of development of secondary sexual characters e.g. Lack of hair growth over face, trunk and axilla So, no beard or moustache and the pubic hairs become sparse and female type (outline become concave instead of convex).
iv. There is no change in the larynx, so the voice does not deepen.
v. Deposition of fat occurs and takes a femine deposition (Buttocks, Hip, Pubis, Breasts).
vi. Lack of muscular development i,e. these are less developed and flabby.
vii. Delay in union of epiphysis, incre- ase in the height (limbs are longer in proportion to trunk)
viii. Skin is pale and tansletile when exposed to suns rays.

Effect of removal of testes after puberty

The effects are variable in different subjects. Some effects are more pronounced than others.

These changes are :

i. Seminal vesicle and prostate atrophy as its development and maintenance depend on the secretion of testosterone which is lacking.
ii. Loss of sexual desire and activities in most subject, those these persist in few.
iii. Falling of hair occurs along with the tendency to baldness sparseness of beard and moustache and recession of convex hair margins of the pubis.
iv. Sometimes feminine deposition of fat occurs.
v. No change in the size of penis.
vi. No change in the voice.
vii. Psychological upset in conveniences the subject greatly.

Female Reproductive System

Female reproductive organs : The female reproductive organs are classified in to two groups :

A. *Primary sex organs :* Ovary
B. *Accessory sex organs :*
   1. External geni talia (valva)
   2. Vagina
   3. Uterus
   4. Uterine tube
   5. Bartholins gland.

Female Hormonal system

1. *A hypothalamic releasing hormone :*
   a. Gonadotropin releasing hormone (Gn RH), previously also called luteinizing hormone-releasing hormone.
2. The anterior pituitary hormones : Which are secreted in response to the releasing hormone GnRH from the hypothalamus.
   a. Follicle stimulating hormone (FSH)
   b. Luteinizing hormone (LH).
3. Ovarian hormones : Which are secreted by the ovaries in

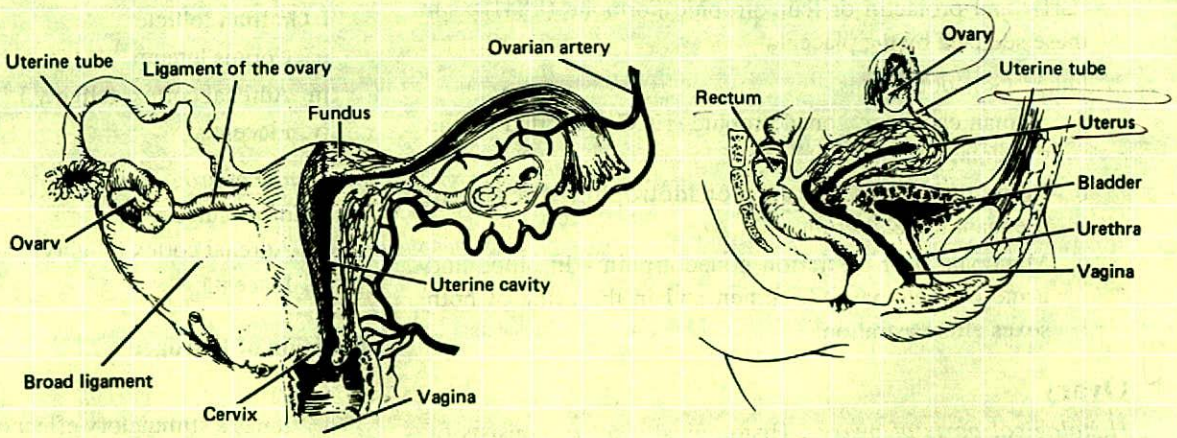


Fig. 9-5. *Female Reproductive System.*

response to the two hormones from the anterior pituitary gland.

a. Estrogen (secreted by the graafian follicles and corpus luteum).
b. Progesterose (Secreted by the corpus luteum)
c. Inhibin (Granulosa cells of the corpus luteum).

(Ref. Guyton & Hall-11th edition; page 1011)

Secondary sexsual character of female

i. Onset of menstrua tion.
ii. Enlargement of breast.
iii. Change in voice (high pitched low frequency)
iv. Maturation of female sex organs.
v. Appearance of pubic and axillary hair.
vi. Enlargement of pelvis in all diameter (Gynaecoid pelvis)
vii. Feminine distribution of subcutaneous fat.
viii. Attraction to the oposite sex.

Phases of reproduction in female

There are two phases :

1. Preparation of the female body for conception and gestation.
2. The period of gestation.

(Ref. Guyton & Hall-11th edition)

Q. **What is sex hormone? Do you think FSH & LH are sex hormone?**

Ans. Hormones which bring about the changes of sex character of male and female is called sex hormone.

Indirectly FSH and LH are sex hormone. Because these bring about the changes in the sex character through gonad. Actually these are gon adotropic hormone.

Gonadotrophic hormone

The Gonadotrphic hormones are so named, because they have profound actons on the gonads and sexual activities of both sex.

They include :

1. Follicle stimulating hormone (FSH), Luteininzing hormone (LH) and prolactin or leuteotrophic hormone (LTH)- all these seereted by the placenta.
2. Other Gonadotrophins -
   a. Human chorionic gonadotrophic (HCG) - secrted by the placenta.
   b. Pregnant mare's serum gonadotrophin -Presant in pregnant mare's serum.
   c. Manopausal or castration gonadotrphin - In blood and urine of menopaused women and in the urine of both sexes after castration.

Ovary

Histological parts of ovary : Histotogically ovary consists of two parts .

i. Cortex or Outer portion.
ii. Medulla or Inner portion.

Cortex : It contains :

1. Germinal epithelium
2. Tunica albicans.
3. Stroma
4. Follicles at various stages -
   a. Primary or primordial follicle
   b. Growing follicle and
   c. Mature graafian follicle.
5. Corpus luteum
6. Interstitial cells.

Medulla : *It contains :*

1. Loose connective tissue
2. Elastic tissue
3. Smooth muscle fibres
4. Blood vessels, lymphatics and nerve fibres.

Functions of the Ovary

It has both exocrine and endocrine function-

1. Exocrine function : Formation of mature ova.
2. Endocnine function : Secretion of four homones :
   a. Oestrogen - Secreted by the Graafian follicles.
   b. Progesterone - Secreted by the corpus luteum.
   c. Androgen.
   d. Relaxin.

Hormone of ovary

Hormones of the ovary are :

1. Estrogen
2. Progesterone
3. Androgen
4. Relaxin.

Source of estrogen and progesterone in female

a. *Source of estrogen :*
   i. Graffian follicle
   ii. Corpus luteum
   iii. Adrenal cortex (slighty)
   iv. Placenta.

b. *Source of progesterone :*
   i. Corpus luteum
   ii. Adrenal cortex (slighty)
   iv. Placenta.

Function of Estrogen

1. *On ovary :*
   i. It has a stimulatory effect on follicular growth.
   ii. It also causes development of gonad in female foetus.

2. *On Fallopian Tube :*
   i. It stimulate musculature and promotes the motility and contractility of the tube.
   ii. It stimulate the epithelium and increases the tubular secretion of the tube.
   iii. It increases the cilliary movement of the tube.
3. *On uterus :*
   i. It causes prolife rative phase of endometrium.
   ii. It increases the motility and sensitivity of myometrium to the oxytocin.
   iii. It increases the size of uterus 2 -3 folds.
4. *On vagina :*
   i. It enlarges the vagina to adult size.
   ii. It causes proliferation and stratification of vaginal epithelium .
5. *On breast :*
   i. Development of the stromal tissues of the breasts.
   ii. Growth of an extensive ductule system of the breasts.
   iii. Deposition of fat in the breasts.
6. *Other effect :*
   i. It causes development of female secondary sexsual character.
   ii. Estrogen increases the total body protein, which evidenced by a slight positive nitrogen balance.
   iii. It causes deposition of large quantities of fat in the subcutaneous tissues, breasts and buttock & thighs.
   iv. It causes the skin to become more vascular, soft and smooth.
   v. It increases the osteoblastic activity of bone and help in rapid growth of bone.
   vi. It stimulates the union between epiphysis and diaphysis.

(Ref. Guyton & Hall-11th edition; page 1017)

N.B. Estrogen mainly promote proliferation and growth of specific cells in the body and are responsible for development of most secondary sexual characteristics of the female.

(Ref. Guyton & Hall-11th edition; page 1016)

Function of Progesterone

1. *On uterus* :
   i. It causes secretory phase of endometriun and preparing the uterus for implantation.
   ii. It decreases the contractility of gravid uterus. Thus prevents expulsion of the implanted ovum.
   iii. It causes development of decidual cell in endometrium which provides nutrition to early embryo.
2. *On fallopian tube :* It increases the tubal secretion and provide nutrtion to zygot before its implantation.
3. *On breast :*
   i. It promote the proliferation of the lobule and alveoli of breast.
   ii. It prepared the breast for lactation.
4. *On Vagina :* It induces cellular proliferation and increased secretion of vaginal epithelium.
5. *On electrolyte balance :* Progesterone causes mild salts and water retention.
6. It has slight protein catabolic actvity.

(Ref. Guyton & Hall-11th edition; page 1018)

N.B. Progestins is concerned almost entirely with final preparation of the uterus for pregnancy and the breasts for lactation.

(Ref. Guyton & Hall-11th edition; page 1016)

Sources of testosterone in woman

1. Ovaries : Secret small quantities of testosterone as well as androstenedione and DHEA (Dehydro epiandrosterone).
2. Suprarenal gland (Zona reticularis of cortex) secrete DHEA and androsterone.

All these hormones enter the circulation. DHEA and androstenedione then enter into the liver (also other tissues) and converted into testosterone and also re-enter into the blood.

Actions of testosterone in woman :
   i. It may be the sex desire of women.
   ii. It causes appearance of pubic and axillary hairs.
   iii. It causes acne vulgaris.

Q. **What is ovulation? How does it occur?**

Ans. Ovulation is the process by which a mature ovum surrounded by cumulus oophorus cells is discharged from the graafian follicle by rupturing the wall of ovary.

Ovulation occurs 14 days before the onset of the first day of next menstruation. Shortly before ovulation the protruding outer wall of the follicle swells rapidly and in the center a small area called stigma protude like a nipple. The fluid begin to ooze from the follicle through the stigma and the follicle become smaller because of loss of fluid, then the stigma ruptures widely and the ovum evaginated into the abdomen.

(Ref. Guyton & Hall-11th edition; page 1014)

Initiation of Ovulation

Approximately two days before ovulation, the quantity of LH secreted by the anterior pituitary increases. This LH at first stimulate theca externa (capsule of the follicle. which form a proteolytic enzyme that cause dissolution and consequent weakening of the capsular wall, resulting in the further swelling of the entire follicle and degeneration of the stigma. Simultaneously, there is rapid proliferation of blood vessels into the follicle wall and secretion of prostaglandin by follicular tissue occur. These two effects in turn causes plasma

transudation into the follicle swelling.

Finally, the combined follicular swelling and simultaneous degeneration of stigma causes follicle rupture with discharge of ovum.

(Ref. Guyton & Hall-11th edition; page 1015)

Determination of ovulation time

It can be determined by -

A. *Direct method :*
   1. Observation of the ovary.
   2. Results of intercourse at different times of menstrual cycle.
   3. Ovulation pain : A slight pain felt on the side in which ovary has discharged the ovum.

B. *Indirect method :*
   1. Alteration of basal temperature : After ovulation temperature rise by 0.3°C-0.5°C.
   2. Estimation of urinary excretion of hormones : Excretion of oestrogen and pregnanediol in urine rises during and after ovulation respec-tively.
   3. Estimation of plasma gonadotropin level (FSH falls and LH high) and oestrogen level high.
   4. Use of ultra sound scanning.

Hormonal control of the maturation of ovum

Control of maturation of ovum : Early maturation is chiefly controlled by FSH, but for full maturation both FSH and L.H are necessary.

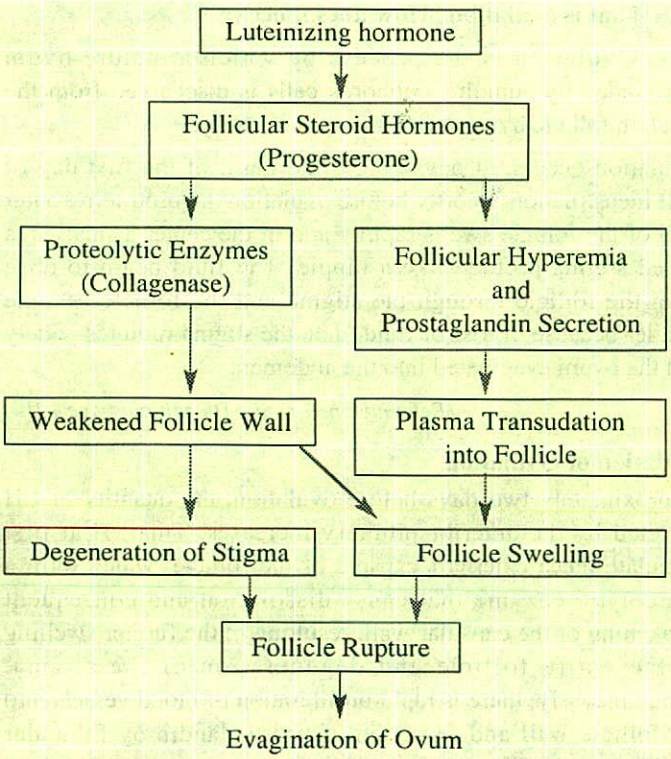


Fig. 9-6. *Postulated mechanism of ovulation.*

Ovulatory surge of LH & FSH

Approximatly 16 hours before ovulation, the rate of secretion of LH by the anterior pituitary increases 6-10 fold and that of FSH increases up to 2 - 3 fold. These two homone act synergistically to cause ovulation (but LH has some specific role). After ovulation the corpus luteum secrets oestrogen and progesterone that decreases the LH and FSH secretion. This phenomenon of sharp rise and fall of LH & FSH secretion is called ovulatory surge of LH & FSH.

(Ref. Guyton & Hall-11th edition; page 1014)

Ovultory surge of LH

Approximately 18 hours before ovulation, the rate of secretion of LH by the anterior pituitary increases markedly (6-10 fold). This causes the ovulation to occur . After ovulation the corpus luteum secretes estrogen and progesterone that decreases the LH secretion. This phenomenon of sharp rise and fall of LH secretion is called ovulatory surge of LH or LH surge.

(Ref. Guyton & Hall-11th edition; page 1014)

Ovarian cycle

The regular maturation of a group of primordial follicle and the periodic sheding of an ocyte, constitute a cyclic change in the ovary , is called ovarian cycle.

It has two phases :

a. *Follicular phase :* In this phase follicle ripen and discharge. At puberty, the rate of secretion of FSH and LH by anterior pituitary increases. The effect of this rapid proliferation of granulosa cell and many spindle cell from ovarian interstisium collect outside the granulosa, form a layer called theca. It has two sublayers. An outer theca externa highly vascular connective tissue layer and an inner theca interna, cellular layer. As development proceeds, irregular fluid filled spaces appear between the follicular cells, which coalesce to form antrum folliculi and the fluid is called liquor folliculi. The follicular cells surrounding the ocyte is known as cumulus oophorus and the rest situated peripherally around the liquor folliculi, called stratum granulosum. Then graafian follicle is formed and ovulation occurs.

b. *Luteal phase :* After ovulation, the remaining granulosa cell become vascularized, yellow in colour and form corpus luteum which then secrete estrogen and progesterone . Corpus luteum is of two types :
   i. Corpus luteum of menstruation.
   ii. Corpus luteum of pregnancy.

Regulation of Ovarian Cycle

Ovarian cycle is regulated by both hormonal and nervous control.

Hormonal regulation :

i. The anterior pituitary secretes FSH and LH FSH initiate the

growth of ovarian follicle and LH helps in final maturation of follicle and ovulation.

Theca cell of graafian follicle secrete large quantities of estrogen that stimulate anterior pituitary to secret LH and inhibit the secretion of FSH.

ii. After ovulation, corpus luteum secretes estrogen and progesterone which then inhibit FSH and LH secretion by feed back mechanism.

Nervous regulation : Hypothalamus secrete FSHRF and LHRF. These two factors act on ant. pituitary which then release FSH and LH. This two hormone inturn maintain normal ovarian cycle.

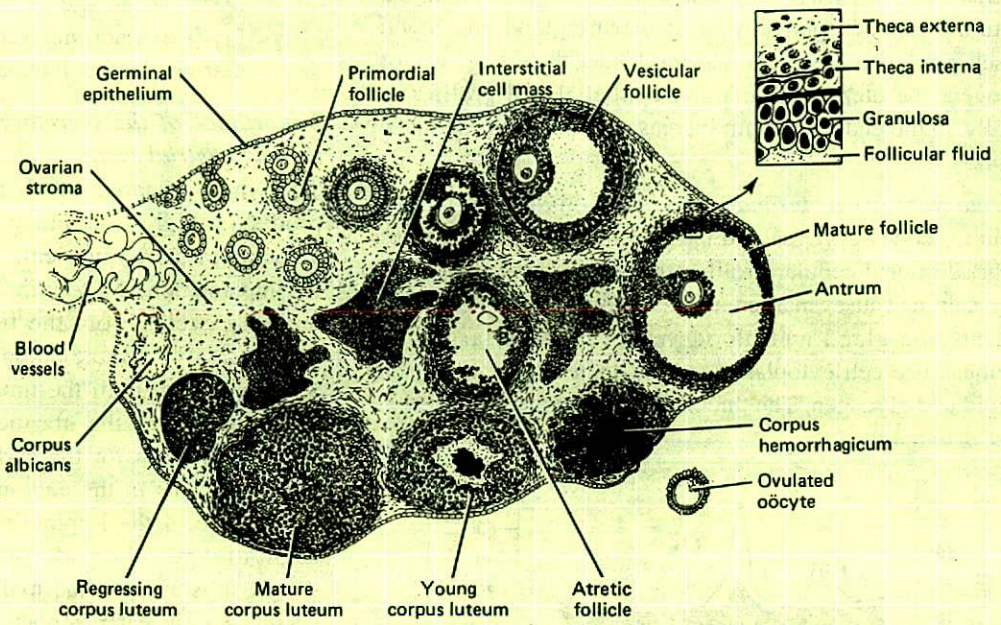


Fig. 9-7. *Diagram of mammalian ovary, showing the sequential development of a follicle, formation of a corpus luteum and in the centre, follicular atresia. A section of the wall of a mature follicle is enlarged at the upper right. The interstitial cell mass is not prominent in primates.*

Q. **What is anovulatory cycle? How this occur?**

Ans. Due to the lack of sufficient amount of luteinizing hormone (LH) sometime ovulation does not occurs in a menstrual cycle and this is known as anovulatory cycle.

If we inhibit the anterior pituitary gland by administration of high doses of progesterone and low doses of estrogen, which causes the decrease secretion of LH. as a result anovulatory cycle occur. It mainly occurs at the early stage of menarche, during menopause and by using contraceptive pills.

(Ref. Guyton & Hall-11th edition)

Effects of removal of ovaries after puberty

i. Uterus become almost infantile type.
ii. Vagina become smaller and vaginal epithelium become thin.
iii. The breast atrophyed and become pendulous.
iv. Atrophy of the valvar structure.
v. Pulic hair become thinner.
vi. Loss of reproductive funtion.
vii. Cessation of menstruation.

Histogical structure of uterus

Histologically uterus composed of three layers. it also contains glands vessels and lymphatics. The layers of uterus are -

1. *Perimetrium* : It is the outer serous coat.
2. *Myometrium* : It is the middle muscle coat. It is consists of interlacing bundles of smooth muscles segmented by fibrous tissue. It is divisible into 3 layers :
   a. Outer longitudinal fibres
   b. Intermediate oblique fibres, arranged in cross spiral fashion.
   c. Inner circular fibres.
3. *Endometrium* : Inside the myometrium is the mucous membrane, called endometrium. It contains glands. At the seeretory phase of menstrual cycle, it contains three layer -
   a. Basal layer
   b. Spongy layer
   c. Compact layer.

Menstrual cycle

The monthly rhythmic changes in the rates of secretion of female hormones and corresponding changes in ovaries and sexual organ as well is known as menstrual cycle. May be regared as periodic preparation for fertilization and pregnancy.

(Ref. Guyton & Hall-11th edition)

Signaficance of menstrual cycle :

i. Only one mature ovum is released from the ovary in each cycle so that one foetus is form.

ii. Prepared the endometrium for implantation.

Stages or phases of menstrual cycle :

1. *Proliferative or estrogenic phase :* After menstru- ation, the stratum basali, deeper portion of uterine gland and blood vessels remain at the endometrium. Under the influe -nce of estrogen, the uterine stroma and epithelial cell proliferate rapidly so the endomet- rium increases in thickness about 3-4 mm.
2. *Secretory or progesteronal phase* : In this phase, corpus luteum secretes estrogen and progesterone. Estrogen causes slight additional cellular proliferation of endometrium while progesterone causes marked swelling and secretory changes. The uterine gland and blood vessel become large and tortuous. The cell cytoplasm contain secretory granule rich in lipid and glycogen. The thickness become 5-6 mm.

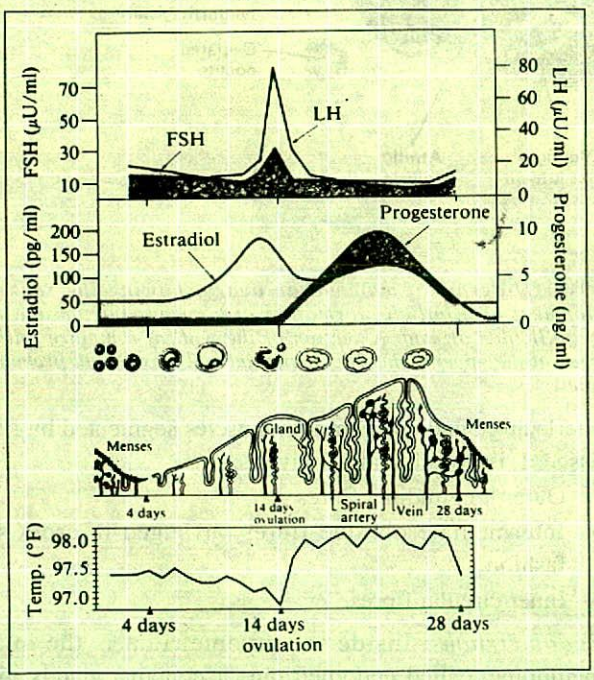


Fig. 9-8. *Variation in the plasma levels of FSH, LH, estradiol and progesterone with different phages of menstrual cycle.*

3. *Menstrual phase (Mechanism of menstrual bleeding)* : The menstrual bleeding occurs when the ovum fails to fertilize and blood estrogen and progesterone level falls due to the degeneration of corpus luteum .

   Approximately two days before menstruation the quantity of estrogen and progesterone sharply decreases which causes involution of endometrium due to decreased hormonal stimulation. This involution causes release of vasoconstrictor material. Due to-

   i. Release of some vasoconstrictor substance .

   ii. Withdrawal of estrogen which is a vasodilator, the tortuous blood vessels become vasospastic and necrosis of endometrium occur. As a result blood sweeps into the vascular layer of endometrium and a haemorrhagic area will grow.

   Gradually the necrotic outer layer will separate from the uterus at the site of haemorrhage and all the superficial layer of endometrium along with blood vessels and uterine gland will expelled out by uterine contraction.

Importance of the secretory phase *(progestational phase)* ***of the endometrial cycle*** :

The whole purpose of all these endometrial changes is to produce a highly secretory endometrium that contains large amounts of stored nutrients to provide appropriate conditions for implantation of a *fertilized* ovum during the latter half of the monthly cycle. From the time a fertilized ovum enters the uterine cavity from the fallopian tube (which occurs 3 to 4 days after ovulation) until the time the ovum implants (7 to 9 days after ovulation), the uterine secretions, called *uterine milk*, provide nutrition for the early dividing ovum. Then, once the ovum implants in the endometrium, the trophoblastic cells on the surface of the implanting ovum (in the blastocyst stage) begin to digest the endometrium and absorb the endometrial stored substances, thus making great quantities of nutrients available to the early implanting embryo.

(Ref. Guyton & Hall-11th edition; page 1019)

Hormonal control of secretory phase *(progestational phase)* ***of the endometrial cycle*** :

During most of the latter half of the monthly cycle after ovulation has occurred, progesterone and estrogen together are secreted in large quantity by the corpus luteum. The estrogens cause slight additional cellular proliferation in the endometrium during this phase of the endometrial cycle, whereas progesterone causes marked swelling and secretory development of the endometrium. The glands increase in tortuosity an excess of secretory substances accumulates in the glandular epithelial cells. Also, the cytoplasm of the stromal cells increases; lipid and glycogen deposits increase greatly in the stromal cells; and the blood supply to the endometriurn further increases in proportion to the developing secretory activity, the blood vessels becoming highly tortuous. At the peak of the secretory phase, about 1 week after ovulation, the endometrium has a thickness of 5 to 6 millimeters.

(Ref. Guyton & Hall-11th edition)

Menstration

The cyclic discharge of blood, unfertilized ovum and certain other substances from uterus through vagina in the female reproductive life at an average interval of 28 days is called menstruation.

a. *Composition of menstrual blood* :
   i. Blood 30-70 ml.
   ii. Stratum compactum and spongiosum of endometrium.
   iii. Mucous

iv. Unfertilized ovum.
v. Leucocytes.
vi. Fibrinolysin.
vii. Some chemical substance like glycogen.

b. *Nature of menstrual blood* :
i. It is liquid, pale, reddish brown in colour.
ii. Its smell is fishy like.
iii. It is non clotting due to absence of clotting factor and presence of fibrinolysin which acts as anticoagulant.

Q. **Why menstruation does not occur during pregnancy?**

Ans. If fertilization does not occur, menstru-ation occurs at the 14 days after ovulation due to sudden fall of blood estrogen and progesterone level.

But if fertilization and implantation occur, the trophoblastic cell of the placenta secretes large quantities of chorionic gonadotropin which prevent the involution of corpus luteum. This corpus luteum secretes large quantites of estrogen and progesterone which continue the growth of endometrium and prevents the menstruation. So, menstruation does not occur during pregnacy.

Menarche : Means the onset of menstruation . It is at about 12 to 14 years.

Menopause

I. *Definition* : Cessation of menstrual cycles due to unresponsiveness of the ovaries, naturally occurring about the age of 45-55 years is called menopause.

II. *Characteristics* :
a. Estrogen deficiency
b. High levels of plasma FSH and LH
c. Features of estrogen deficiency
i. Hot flashes
ii. Vaginal dryness
iii. Breast atrophy
iv. Weight gain
v. Loss of libido.

Cornification : Changes of mucosa of vagina, uterus, and uterine tube is called cornfication,
These changes include-
i. Stratification
ii. Increase mitotic activity.
iii. Deposition of glycogen.

Amenorrhoea : It means the absence of menstruation.

Cause :
i. Before puberty
ii. After menopause
iii. During pregnacy
iv. Some time during lactation.

Dysmenorrhoea : It means painfull or difficult menstruation.

Reproductive period : It is the life of female between menarche and menopause.

Danger period : From 9 to 17th days of menstruation or roughly the middle week of menstruation. Because in this time there is chance of fertilization, if ovum comes in contact with mature sperm.

Viable period : It is the 7th month of pregnancy. In early stage of pregnancy the pulmonary circulation of foetus is less and is just adequate for providing nutrition, with further development, pulmonary circulation starts. At 7th month it is rich enough to supply adequate O_2 for the survival of the subjects. So, this stage is called viable period.

Primodial follicle : The primodial ova surrouded by a single layer of granulosa cells, is called primodial follicle.

(Ref. Guyton & Hall-11th edition)

Germinal epithelium : During foetal life outer surfacr of ovary covered by a layer of cells which embryologicaly derived from germinal ridge, is called germinal epithelium.

(Ref. Guyton & Hall-11th edition)

Ova count at different stage of life

At the 30th week of gestation the number of ova reaches about 7 million. But most of them degenerate. So that less than 2 million are present in the two ovaries at birth and only 300,000 to 400,000 at puberty. Then during all the reproductive years of women from about 13 to 46 years of age, about 400 of these follicle develope enough to expell their ova- one each month, the remainder degenerate. At the menopause, only a few primodial follicle remain in the ovaries, & even these degenerate soon after.

(Ref. Guyton & Hall-11th edition)

Ogenesis : In the female, the maturation process from primitive germ cell to mature gamate is known as ogenesis.

(Ref. Lang Man 5th page 17)

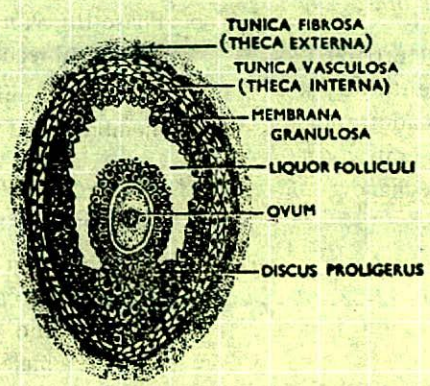


Fig. 9-9. *Vesicular or Graafian follicle*

Graafian Follicle

The compeletly developed primary ocyte surrounded by many layer of cells, containing vesicle is known as graafian follicle.

The graafian follicle comprises the following structure from outer to inner :

i. *Theca externa :* It is an outer fibrous layer which gradu ally merges with the ovarian stroma.

ii. *Theca interna or theca gland :* It is an inner cellular layer which is rich in blood vessel.

Function : It is the main source of oestrogen, the female sex hormone, that regulates the function of the reproductive organ.

iii. *Stratum granulosum cells.*

iv. *Cumulus oophorus :* The ovum together with surrounding granulosa cells is called the cumulus oophorus.

v. *Zona pellucida :* It is an acellular material consisting of mucopolysaccharide deposited on the surface of the ocyte.

(Ref. Lang Man 5th page 12)

Corpus Luteum

It is a folded and collapsed new ovarian structure formed from the remaining position of the graafian follicle after ovulation. It is a temporary endocrine gland.

Types : It is of two types -

i. Corpus luteum of menstruation.

ii. Corpus luteum of pregnancy.

Mechanism : During the first few hours after the expulsion of the ovum from the follicle, the remaining granulosa cells changes rapidly. Under the influence of LH yellow pigment grows in these cell and change into Luteal cell. These cell grow to a diameter two or more times as large as the granulosa cells and become filled with lipid inclusions. This process is called leutinization.

(Ref. Guyton & Hall-11th edition)

Corpus Luteum of menstration : If fertilization does not occurs corpus luteum reaches maximum development about 9 days after ovulation. It can easily recognised as a yellowish projection on the surface of the ovary. Subsequently the corpus luteum decrease in size through the degeneration of the luteal cell, which is known as corpus luteum of menstruation.

After the degeneration it forms a fibrotic mass known as corpus albicans.

Secretion :

i. Progesterone

ii. Estrogen

iii. Inhibin. *(Ref. Lang Man 5th 22)*

Corpus Luteum of pregnancy : If the ocyte is fertilized, degeneration of the corpus luteum is prevented by a gonadotropic hormone (human chorionic gonadotropin) secreted by the trophoblast of the developing embryo, it continues to grow and forms corpus luteum of pregnancy.

Secretion :

i. Progesterone

ii. Estrogen. *(Ref. Lang Man 5th 22-23)*

Stimulation of female sexual act

1. *Psychic stimulation :* Thinking of erotic thoughts etc.

2. *Local sexual stimulation :* Clitoris, nipple, vulva, vagina, and other perineal region and even the urinary tract.

(Ref. Guyton & Hall-11th edition; page 1023)

Stages of female sexual act

1. *Erection :* During sexual stimulation, the arteriols of the erectile tissue, located around the introitus and into the clitoris dilated, and this allows rapid accumulation of blood in the erectile tissue so that introitus tightens around the penis.

2. *Lubrication :* Bilateral Bartholin's glands located beneath the labia minora, vaginal epithelium and a small amount from the male urethral glands, cause secretion of mucus inside the introitus. This mucus is responsible for lubrication during sexual intercourses for satisfactory masaging sensation.

3. *Orgasm :* When local sexual stimulation as well as psychic stimulation reaches in maximum intensity, cause the female orgasm, called female climax. It is analogous to amission and ejaculation in the male. There occurs rhythmic contraction of the perianal muscle, motility of the uterine and fallopian tube and dilatation of the cervical canal, thus helps to promote fertilization of the ovum.

(Ref. Guyton & Hall-11th edition; page 1023)

Fertilization

i. *Definition* : Fertilization is the process by which male and female gametes fuse.

ii. *Sites* : Usually it occurs in the ampullary region of the uterine tube.

iii. *Phases* : The phases of fertilization include :

a. Phase-I : *Penetration of the corona radiata by sperm* : Of the 200-300 million spermatozoa deposited in the female genital tract in each ejaculation, only 300-500 reaches the site of fertilization. Only one of them is needed for fertilization, and it is thought that the others aid the fertilizing sperm in penetrating the barriers protecting the female gamete.

b. Phase-II : *Penetration of the zona pellucida* : By acrosomal reaction.

c. Phase-III : Fusion of the oocyte and sperm cell membranes.

iv. *Results of fertilization* :

a. Restoration of the diploid number (46) of chromosomes

b. Determination of the sex of the new individual. An X chromosome carrying sperm will produce a female (XX) embryo, and a Y chromosome carrying sperm will produce a male (XY) embryo.

c. Initiation of cleavage (a series of mitotic divisions).

Pregnancy

i. ***Physiology of pregnancy*** :

a. Spermatozoa reach the tube between 30 minutes and 3 hours after coitus.
Sperm are attracted to the ovum by chemotaxis.

b. *Fertilization* : usually occurs in the ampullary region of the tube.

c. *Blastocyst formation* : Fertilization is followed by blastocyst formation.
The *blastocyst* is carried down the tube by ciliary and peristaltic action and reaches to the uterine cavity.
Duration : Within 3 days (5-6 days after ovulation).

d. *Implantation* : Placement of blastocyst usually into the posterior wall of the endometrium.
Duration : Tt the end of the 1st week.

e. *Trophoblast formation :* It develops from the outermost cells of the blastocyst

f. *Development of placenta* : It provides nutritional connection between mother and embryo.

ii. ***Endocrine changes in pregnancy*** :

a. *Placenta* secretes human chorionic gonadotropin (hCG), which prevent regression of the corpus luteum after fertilization.

b. *Corpus luteum* is enlarged by hCG and secretes estrogen, progesterone and relaxin.
* *Relaxin* : Maintain pregnancy by inhibiting myometrial contraction.
* *Estrogen and progesterone* : Inhibit GnRH secretion, so no new cycle starts.

Corpus luteum function begins to declines after 8 weeks of pregnancy but it persists throughout pregnancy.

c. *Placenta* becomes capable to produce sufficient estrogen and progesterone within 10-12 weeks of pregnancy.

iii. ***Duration of pregnancy*** :

a. 280 days from the first day of the last menstrual period.
b. 274 days : from fertilization.
c. 266 days : from the date of intercourse - if pregnancy has followed a single coitus.

iv. ***Symptoms of pregnancy*** :

a. *Amenorrhoea* : in women with previous regular periods
b. Morning sickness
c. Tenderness and fullness of the breasts
d. Frequency of micturation
e. Later stage : breasts enlargement, abdominal enlargement and feeling of the fetal movement (*quickening*).

v. ***Signs of pregnancy*** :

a. Uterus :
1. Enlargement of the body of the uterus.
2. Softening of the uterus : uterus becomes progressively enlarged.

b. *Foetus* :
1. Palpation of fetal parts; fetal movements may be felt *(absolute sign of pregnancy).*
2. Fetal heart sounds may be heard.

c. Pigmentation on the abdomen breasts and face.

vi. ***Most common tests for pregnancy*** :

a. *Ultrasonography for pregnancy* : It determines the embryonic heart movements within six weeks of the pregnancy *(absolute sign).*

b. *Urine for pregnancy* : Presence of large amount of hCG in the patient urine sample (morning specimen) : It is not absolutely specific for pregnancy.

Physiological changes during pregnancy

Anatomical and physiological changes that occur during pregnancy chiefly involve the genital tract and the breasts. Many other interrelated changes occur in other systems of the body. The most important alterations in maternal physiology during pregnancy include :

a. ***Endocrine and paracrine changes during pregnancy*** :

i. *Human chorionic gonadotrophin* : The *trophoblast* produces large amounts of human chorionic gonadotrophin (hCG), particularly in the first trimester of pregnancy. hCG can be detected in the blood as early as 6-14 days after conception.

ii. *Estrogens* and *progesterone* : Large amounts of estrogens and progesterone are found in the blood and urine during pregnancy.
At first these are secreted by the corpus lutcum and then by the placenta after the 12th week.

iii. The alpha-fetoprotein-AFP (embryonic origin) concentrations in the maternal serum are increased by highest concentrations is in amniotic fluid.

iv. Other maternal endocrine changes include-
1. Hpertrophy of the anterior pituitary lobe
2. Thyroid enlargement
3. Increased BMR
4. Increased concentration of adrenal hormones in the blood and urine.

b. ***Meternal metabolic changes during pregnancy*** :

i. Body weight : It increases 7-17 kg

ii. Considerable salt and water retention at term : 3300 ml.
1. Increase in intracellular water : 550 ml
2. Increase in extracellular water :
Intravascular (plasma) : 900 ml
Extravascular : 1850 ml.

iii. Increase basal metabolic rate-BMR : 10-25%

iv. Increase total need for calories

v. Plasma levels of triglyceride, cholesterol and free fatty acids rises.

vi. Increased demand for iron and calcium and proteins.

c. ***Hematological changes during pregnancy*** :

i. *Blood volume* : is increased during pregnancy by about 30 percent.

ii. *Red cells* : Total number and volume of red cells increase by about 20 percent

iii. *Hemoglobin* : Total amount of hemoglobin in the maternal blood is increased.

iv. *ESR* : is much increased (up to 100 mm in the 1st hour are not unusual).

d. ***Changes in the different systems of the body during pregnancy*** :

i. *Changes in the CVS* :

1. *Cardiac output* : Rises from 4-5 to 6 liters per minute during the first ten weeks of pregnancy.
2. *Systolic blood pressure* : is unaltered during normal pregnancy.
3. *Diastolic pressure* : is reduced in the first and second trimester, returning to non-pregnant levels by term.
4. Heart rate rises by between 6-8 beats per minute.

ii. *Changes in the respiratory system* :

1. *Pulmonary ventilation* : is increased by about 40 percent as a result of increased tidal volume.
2. *Oxygen requirements* : only increased by 20 percent and PCO_2 is decreased.

iii. *Changes in the alimentary tract* :

1. Nausea
2. Morning sickness.
3. Appetite and thirst increase.

iv. *Changes in the genital tract* :

1. *Uterus* : increase in size with enormous growth of the myometrium.
   * Weight of the uterus : increased upto 1 kg (in non-pregnant 65 g only).
   * Cervical mucus glands : Increased vascularity and secretions of cervical mucus glands.
2. *Vagina* : vascularity increased; increased watery vaginal secretions.

iv. *Changes in the urinary tract* :

Kidney :

* Increased GFR and renal plasma flow.
* A progressive fall in the plasma creatinine levels
* A progressive fall in the blood urea levels
* Increased salt and water retention due to increased aldosterone, renin and angiotensin II and angiotensin I.
* Increased frequency of micturation.

v. *Changes in the skin* :

1. *Abdominal skin* : become stretched and form striae gravidarum.
2. *Pigmentation* on the
   - abdominal wall ***(linea nigra)***
   - areolae of the breasts
   - face, forehead or cheeks.

   The *cause of these changes* in unknown, but may be related to estrogen, progesterone, adrenal hormones or an increase in melanocyte stimulating hormone (MSH).

e. ***Emotional changes during pregnancy.***

Pregnancy tests

1. Friedman test
2. Galli manini test
3. Hoggben test
4. Aschheim Zondek test .
5. Immunological test
6. Kupperman test
7. Haemagglutination test.

Physiological basis of pregnancy test : During the early stage of pregnancy female placenta secretes large amount of chorionic gonadotropins which come out in urine. So, tests are carried out with the patients morning urine and note whether it contain such hormone or not.

Immunological pregnancy test: Immunological pregnancy test based on the precipitation of latex particle coated with antibodies due to chorionic ganadotropin hormone. Antibodies are produced after administration of human gonadotropin in rabbits. Antiserum taken from this rabbits and are used to detect the presence of chorionic gonadotropin in pregnant women's urine with the help of compliment fixation test.

Labor pain

With each uterine contraction, the mother experiences considerable pain. The cramping pain in early labor is probably caused mainly by hypoxia of the uterine muscle resulting from compression of the blood vessels in the uterus. This pain is felt when the visceral sensory *hypogastric nerves*, carry the visceral sensory fibers leading from the uterus.

However, during the *second stage of labor*, when the fetus is being expelled through the birth canal, much more severe pain is caused by cervical stretching, perineal stretching, and stretching or tearing of structures in the vaginal canal itself. This pain is conducted to the mothers spinal cord and brain by somatic nerves instead of by the visceral sensory nerves.

(Ref. Guyton & Hall-11th Edition; page 1038)

Parturition

It is the process of giving birth.

Stages of Labour (parturition) :

i. *1st stage of labour :* It starts from the onset of true labour

pain and ends with full dilatation of the cervix.

ii. *2nd stage :* It starts from the full dilatation of the cervix and ends with expulsion of the foetus from the birth canal.

iii. *3rd stage :* It begins after the expulsion of the foetus and ends with expulsion of the placenta and membranes.

(Ref. Obstetrics D.C. Dutta. 2nd. page 121-125)

Role of Oxytocin in Parturition :

Increase in oxytocin receptors
↓
Prostaglandins
↓
Uterine contractions
↓
Dilation of cervix & distention of vagina
↓
Stimuli from cervix & Vagina
↓
Incereased secretion of oxytocin

Puerperium

It is the period following child birth during which the body tissues, specially the pelvic organs revert back approximately to the prepregnant state both anatomically and physiologically.

Puerperium begins as soon as the placenta is expelled and lasts for approximately 6 weeks.

(Ref. Obstetrics D.C Datta. 2nd-157)

Placenta

Placenta is a flattened, disscoidal mass with circular or oval outline. The placenta is essentially a fetal organ. At full term, the placenta has a diameter of 15-25 cm, is approximately 3 cm thick, and has a weight of about 500-600 gm.

It is an organ in which blood vessels of the embryo are brought into relationship with the blood of the mother.

i. ***Components of placenta*** : The placenta consists of-
   a. Chorionic frondosum (villous chorion)
   b. Decidua basalis
   c. Intervillous lack of maternal blood
   d. Cytotrophoblast cells.

ii. ***Functions of placenta*** : Placenta is the only means of transfer of anabolites and catabolites and, as such, is the main interface between the fetus and the outside world.
   The main functions of the placenta are :
   a. Exchange of gases
   b. Exchange of nutrients and electrolytes
   c. Transmission of maternal antibodies, providing the fetus with passive immunity
   d. Production of hormones
   e. Forms a protective barrier against transfer of infection to the fetus
   f. Detoxification of some drugs.

Exchange of gases : O_2, CO_2 and CO is exchanged by simple diffusion. At term, the fetus extracts 20-30 ml of oxygen per minute from the maternal circulation. The amount of oxygen reaching the fetus is primarily dependent on delivery and not diffusion.

Exchange of nutrients and electrolytes : Amino acids, free fatty acids, carbohydrates, and vitamins exchange occur rapidly and increases as pregnancy advances.

Transmission of maternal antibodies : Maternal antibodies are taken up by pinocytosis by the syncytiotrophoblast and subsequently transported to fetal capillaries. In this manner, the fetus acquires maternal antibodies of immunoglobulin G (IgG) class against various infectious diseases. The fetus has little capacity to produce its own antibodies until after birth.

iii. ***Placental transport :***
   i. Substances that can cross the placental barrier :
      a. Gases : O_2, CO_2, CO.
      b. Nutrients : Carbohydrates, FAs, triacylglycerol, cholesterol, proteins.
      c. Electrolytes : Na^+, K^+, Ca^{++}, Mg^{++}.
      d. Amino acids, nucleic acids, urea, uric acid.
      e. Water.
      f. Low molecular weight substances (<1000) i.e anesthetic drugs.
      g. Hormones : Thyroid hormones, estrogens and androgens.
      h. Immunoglobulin : IgG only.
      i. Fetal red cells (nucleated) to maternal blood.
   ii. *Substances that cannot cross the placental barrier* :
      a. Substances of very high molecular weight (>1000).
      b. Hormones : Insulin, parathyroid hormones, ADH, oxytocin.
      c. Immunoglobulin : IgA and IgM.

iv. ***Hormones of the placenta*** : Placental hormones maintain pregnancy. In all probability, all hormones are synthesized in the *syncytial trophoblast* and are secreted into the maternal blood.
   Placental hormones are :
   1. Human chorionic Gonadotropin (hCG)
   2. Progesterone
   3. Estrogenic hormones (predominently estriol)
   4. Chorionic growth hormone- Prolaction (CGP)
   5. Human chorionic somatomammotropin (hCS)
   6. Relaxin
   7. Others : GnRH, lnhibin and TSH etc.

Human chorionic Gonadotropin (hCG) : hCG is a glycoprotein secreted by the syncytiotrophoblast.

i. *Plasma detection* : hCG can be detected in the maternal plasma by radioimmunoassay as early as 6 days after fertilization of the ovum and found in urine as early as 14 days after conception.

ii. *Peak concentration* : It reaches its peak concentration in the blood and urine at 12 weeks of gestation.

iii. *Importance* :

a. hCG support the corpus luteum untill the placenta produces amounts of progesterone sufficient to support the pregnancy.

b. The presence of hCG in the urine forms the basis of the routine tests for pregnancy *(hCG is not absolutely specific for pregnancy).*

Double Bhor effect

Bohr effect, enhances transport of oxygen by the fetal blood. That is, hemoglobin can carry more oxygen at a low Pco_2 than it can at a high Pco_2 . The fetal blood entering the placenta carries large amounts of carbon dioxide, but much of this carbon dioxide diffuses from the fetal blood into the maternal blood.

Loss of the carbon dioxide makes the fetal blood more alkaline, whereas the increased carbon dioxide in the maternal blood makes this more acidic. These changes cause the combining capacity of fetal blood for oxygen to become increased and that of the maternal blood to become decreased.

This forces still more oxygen from the maternal blood while enhancing oxygen uptake by the fetal blood. Thus, the Bohr shift operates in one direction in the maternal blood and in the other direction in the fetal blood, these two effects making the Bohr shift twice as important here as it is for oxygen exchange in the lungs; therefore, it is called the *double Bhor effect.*

(Ref. Guyton & Hall-10th Edition;)

Involution of the uterus after parturition

i. *During the first 4 to 5 weeks after parturition* : The uterus involutes. Its weight becomes less than one half its immediate postpartum weight within 1 week.

ii. *In 4 weeks after parturition* : If the mother lactates, the uterus may be as small as it had been before pregnancy. This effect of lactation results from the suppression of pituitary gonadotropin and ovarian hormone secretion during the first few months of lactation.

During early involution of the uterus, the placental site on the endometrial surface autolyzes, causing a vaginal discharge known as *lochia*, which is first bloody and then serous in nature, continuing in all for about 10 days. After this time, the endometrial surface becomes re-epithelialized and ready for normal, nongravid sex life again.

(Ref. Guyton & Hall-11th Edition; page 1038)

Lactation

Definition : The process of formatoin and secretion of milk in the alveoli of breast and its expulsion from mammary gland is called lactation.

Phages of lactation : Lactation include 4 phases-

1. *Mammogenesis :* It means development of breast . Female sexual hormones at puberty act on the stromal tissues , alveoli and ducts of the breast and influenced its development . Estrogen cause devlopment of stoma and duct system. Progesterone is responsible for the development of lobule and alveoli .
2. *Lactogenesis :* It means synthesis of milk . It is initiated by the prolactin and is ***continued by*** the growth hormone, thyroxin and ACTH. This three hormones form a modified solution of carbohydrate, protein and fat etc.
3. *Lactopoesis :* Continuation of lactogenesis by maintaining the secretion of leutotropic hormone (LTH) is called lactopoesis.
4. *Ejection of milk :* When baby sucks the breast, stimulation from nipple passes to hypothalamus which stimulates posterior pitutary to secrete oxytocin. The oxytocin contracts the muscle fibre (myoepithelial cells) of alveoli and duct repeatedly and initiate the ejection of milk.

Role of hormones on lactation *(Mammary gland)*

1. Estrogen : Responsible for the development of stroma & duct system of the brest.
2. Progesterone : Responsible for the development of lobule & alveoli of the brest.
3. Prolactin :
   i. Final development of breast.
   ii. Synthesis and secretion of milk.
4. Oxytocin :
   i. Contraction of myoepithelial cells of breast .
   ii. Ejection of milk.
   iii. Contraction of uterus during parturation .
5. Growth Hormone : It is essential for overall development of breast.
6. Thyroid hormone : Helps in the development of breast and lactation by increasing the metabolism.
7. ACTH : It helps in development of breast.

Mammogenesis

i. *Definition* : It is the process of development of breast.

ii. Stages : It occurs in three phases (stage) :

1. *Quiescent phases (upto puberty) :* Very little growth of mammary tissue is observed in this phases.
2. *Phases of active growth :* With the onset of puberty

under the influence of hormone (Oestrogen and progesterone). Active growth of the gland (deve lopment and proliferation of duct and alveolar system) occur.

3. *Phase of lactation* : During pregnancy further development of the ducts and alveolar systems occurs due to hormones of ovary and placenta. After pregnancy the glands begin secretion of milk under the influence of prolactin.

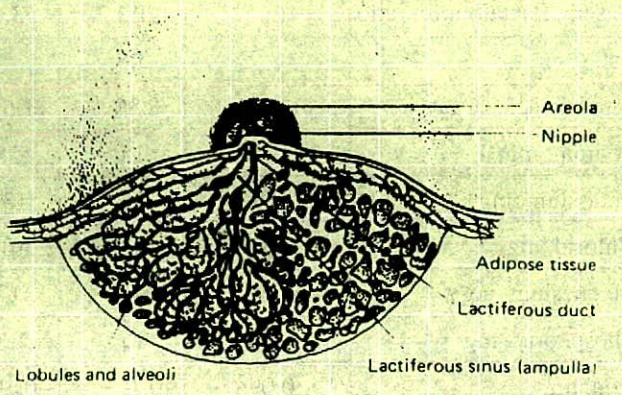


Fig.9-10. *The Breast & its Mammary Gland.*

Regulation of lactogenesis

Immediately after the baby is born, the sudden loss of both estrogen and progesterone secretion by the placenta now allows the lactogenic effect of the prolactin from the mother's pituitary gland. Over the next 1 to 7 days the breast begins to secret copious quantities of milk instead of colostrum.

The secretion of milk requires an adequate secretion of most of the mother's other hormone as well, are growth hormore, cortisol and parathyroid hormone. These hormones are necessary to provide the amino acids, fatty acids, glucose and calcium that are required for milk formatin

Low level of oestrogen & progesterone → anterior pitutary → prolactin → breast → milk scertion.

(Ref. Guyton & Hall-11th edition; page 1039)

Double threshold theory of lactation

After expulsion of the placenta at parturation, there is an abrupt decline in circulating estrogens and progesterone. Lactation is then initiated because :

a. Low progesterone increases prolactin secretion
b. Low estrogens increase prolactin secretion.

High level of circulatory prolactin initiates milk. This is the double threshold theory regarding secretion of milk.

Galactopoaesis

Galactopoiesis means maintenance of lactation. Factors maintaining lactation are :

i. Maternal nutrition
ii. Fluid intake
iii. Hormonal role.

Two neuroendocrine reflexes ensure secretion of prolactin and oxytocin and aids in the maintenance of lactation.

Lactational amenorrhoea

i. *Definition* : Absence of menstruation in women who nurses regularly is called lactational amenorrhoea.

ii. *Duration* : It may last for 25-30 weeks. If no nursing, the women have their first menstrual period 6 weeks after delivery.

iii. Mechenism : Nursing the baby increases the prolactin secretion. Prolactin causes inhibition of GnRH secretion. So inhibit the action of GnRH on anterior pituitary gland. Antagonizes the FSH and LH action on the ovaries. Preventing follicular development. Ultimately no ovulation and so, no luteinization. Decrease estrogen and progesterone output and no meanstrual period.

Process in milk ejection

It is the process by which the milk is ejected or 'let down' from the alveoli to the duct before the baby can obtain it.

The process is caused by a combined neurogenic and hormonal reflex involving the posterior pituitary hormone oxytocin.

When the baby suckles the breast or when cries for milk, sensory impulse are transmitted through somatic nerves from the nipples to the spinal cord and then to the hypothalamus, there causing oxytocin secretion at the same time that they cause prolactin secretion. Oxytocin then carried via blood to the breast, where it causes contraction of the myoepithelial cells that surround the outer walls of the alveoli, and initiates the ejection of milk.

(Ref. Guyton & Hall-11th edition; page 1040)

Diagrammatic representations of milk let-down process :

Suckling of the breasts
↓
Somatic touch receptors are stimulated and generate impulses
↓
Impulses go to the hypothalamus via Bundle of Schultze and mammary peduncle of the spinal cord
↓
Supraoptic and paraventricular nuclei are stimulated
↓
Oxytocin is released from the posterior pituitary
↓
Oxytocin causes contraction of myoepithelial cells
↓
Milk let-down.

Colostrum

The fluid that is secreted the last few days before and first few days after parturation is called *colostrum.*

It contains essentially the same concentrations of proteins and lactose as milk but almost no fat, and its maximum rate of production is about 1/100 the subsequent rate of milk production.

Composition of colostrum : (Units are weight per deciliter)

Component	*Human Colostrum*
a. Water, gm	...
b. Lactose, gm	5.3
c. Protein, gm	2.7
d. Fat, gm	2.9
e. Sodium, mg	92
f. Potassium, mg	55
g. Chlorid, mg	117
h. Magnesium, mg	4
i. Phosphorus, mg	14
j. Iron, mg	0.09[2]
k. Vitamin A, µg	89
l. Vitamin D, µg	...
m. Thiamine µg	15
n. Riboflavin, µg	30
o. Nicotinic acid, µg	75
p. Ascorbic acid, µg	4.4

(Ref. Guyton & Hall-11th Edition and others)

Pre-eclampsia : During the last four months of pregnancy approximately 4% of pregnant women experience a rapid rise in arterial blood pressure associated with loss of large amounts of protein in the urine. This condition is called preeclampsia.

1. *Cause of pre-eclampsia* :
   i. Development of autoimmunity resulting from presence of foetus,
   ii. Excessive secretion of placental or adrenal hormones.
2. *Effect of pre-eclampsia :*
   i. Salt and water retention by the kidney, weight gain and oedema.
   ii. Arterial spasm specially in kidney, brain, liver etc.
   iii Renal blood flow and glomerular filtration decreased.

(Ref. Guyton & Hall-11th Edition)

Eclampsia : It is an extreme degree of preeclampsia occurs shortly before pregnancy, characterized by extreme vascular spasticity throughout the body, clonic convulsions followed by coma, greatly decreased kindney output, malfunction of liver, extreme hypertension and generalized toxic condition of the body.

Treatment : Use of rapidly acting vasodilator drug to decrease the blood pressure normal.

Composition of colostrum and milk.

(Units are weight per deciliter.)

Component	*Human Colostrum*	*Human Milk*	*Cows' Milk*
Water, g	...	88	88
Lactose, g	5.3	6.8	5.0
Protein, g	2.7	1.2	3.3
Casein, Lactalbumin ratio		1.2	3.1
Fat, g	2.9	3.8	3.7
Linoleic acid of fat		8.3%	1.6%
Sodium, mg	92	15	58
Potassium, mg	55	55	138
Chlorid, mg	117	43	103
Magnesium, mg	4	4	12
Phosphorus, mg	14	15	100
Iron, mg	0.09[2]	0.15[2]	0.10[2]
Vitamin A, µg	89	53	34
Vitamin D, µg	...	0.032	0.062
Thiamine µg	15	16	42
Riboflavin, µg	30	43	157
Nicotinic acid, µg	75	172	85
Ascorbic acid, µg	4.4[2]	4.3[2]	1.6[2]

Abnormal conditions that cause female sterility : About one of every six to eight marriages is infertile; in about 60 per cent of these marriages, the infertility is due to female sterillty.

i. *Failure to ovulate* : *Cause-*
   a. Hyposecretion of gonadotropic hormones.
   b. Abnormal ovaries that will not allow ovulation. For instance, thick ovarian capsules occasionally exist of the outsides of the ovaries, making ovulation difficult.

ii. *Endometriosis* : Endometriosis causes fibrosis throughout the pelvis, and this fibrosis sometimes so enshrouds the ovaries that an ovum cannot be released into the abdominal cavity. Often, endometriosis occludes the fallopian tubes, either at the fimbriated ends or elsewhere alone their extent.

iii. *Salpingitis* : This causes fibrosis in the tubes, thereby occluding them.

iv. *Secretion of abnormal mucus by the uterine cervix* : Ordinarily, at the time of ovulation, the hormonal environment of estrogen causes secretion of mucus with special characteristics that allow rapid mobility of sperm into the uterus and actually guide the sperm up along mucous *threads*. Abnormalities of the cervix itself, such as

low-grade infection or inflammation, or abnormal hormonal stimulation of the cervix, can lead to a viscous mucus plug that prevents fertilization.

(Ref. Guyton & Hall-11th Edition; page1024)

Tests :

i. One of the tests of is simply to *analyze the urine for a surge in pregnanediol*, the end product of progesterone metabolism, during the latter half of the sexual cycle, the lack of which indicates failure of ovulation.

ii. Another common test is for the woman to chart her *body temperature throughout the cycle*. Secretion of progesterone during the latter half of the cycle raises the body temperature about 0.5°F, the temperature rise coming abruptly at the time of ovulation.

(Ref. Guyton & Hall-11th Edition; page1025)

Lack of ovulation caused by hyposecretion of the pituitary gonadotropic hormones can sometimes be treated by appropriately timed administration of *human chorionic gonadotropin*, a hormone that is extracted from the human placenta. This hormone, although secreted by the placenta, has almost the same effects as LH and, therefore, is a powerful stimulator of ovulation. However, excess use of this hormone can cause ovulation from many follicles simultaneously; this results in multiple birth, an effect that has caused as many as eight babies (but mostly stillborn babies) to be born to mothers treated for infertility with this hormone.

(Ref. Guyton & Hall-11th Edition; page1024)

Q. **What are the change takes place to pregnant mother's body?**

1. *Weight gain :* The average weight gain is about 24 lbs. of which-

Foetus	: 7 lbs
Amnitotic fluid	: 4 lbs.
Uterus	: 2 lbs.
Breast	: 2 lbs.

2. *Metabolism :* About 15% increases due to several hormone such as TSH, ACTH, GH.
3. *Nutrition :* It also increasees.
4. *Changes in circulatory system :*
   i. Increase blood volume
   ii. Increase blood pressure
   iii. Increase cardiac output.
5. *Respiration :* The rate and depth of respiration increases.

(Ref. Guyton & Hall-11th Edition)

Ways of controlling population

Population can be controlled in various ways as follows-

1. By adopting contraceptive methods-
   a. Barrier methods-
      i. Physical methods : Condom, Cervical diaphragm.
      ii. Chemical method : Foams, Pastes, Jellies etc.
      iii. Combined method : Physical+Chemical method.
   b. Intrauterine devices : Copper - T.
   c. Hormonal methods : Contraceptive pill e.g.-Maya, Ovacon etc.
   d. Post conceptional methods : Menstrual regulation (MR), Menstrual induction (MI) etc.
   e. Miscellaneous or behavioral methods : Sexual abstinence & maintain safe period etc.
   f. Sterilization program : Tubectomy for female and vasectomy for male.
2. By sociological approach : Raising age of marriage to a reasonable limit.
3. Improvement of econonic conditon of the people.
4. Increase recreation facilities
5. Health education.

(Ref. Community medicine- Park)

Q. **What are the functions of Maya pill.**

Ans. It converts the ovulatory cycle into anovulatory cycle, because maya pill contain high doses of progesterone and low doses of estrogen, which inhibits the anterior pituitatry gland for the decrease secreation of L.H. and due to absence of LH no ovulation occurs.

Introduction 9.28 | *Female reproductive system 9.30* | *ovulation 9.31* | *Contraception 9.7*
Male reproductive system 9.28 | *Menstruation &* | *Pregnancy, Labour & Lactation 9.32* | *Menopause 9.33*

Directions : Write T for true & F for false against each of the following statement.

Introduction

Q. 01. **Androgens**
- T a. secretion decreases after the age of 30 in male.
- T b. are secreted by the ovary
- T c. are secreted by adrenal cortex
- F d. inhibits the masculinization
- F e. are secreted by sertoli cells

Q. 02. **Androgen receptors are coded in**
- T a. Long arm of X chromosome
- F b. Short arm of X chromosome
- F c. Long arm of Y chromosome
- F d. Short arm of Y chromosome
- F e. All.

Q. 03. **Which of the following determines the sex of the individual :**
- T a. Genotype only
- F b. Genotype + phenotype
- F c. FSH + LH only
- F e. Any of the above
- F e. All.

Q. 04. **A premature infant is more likely than a full term infant to**
- T a. Excrete urine with a uniform specific gravity
- T b. Suffer from anaemia
- T c. Suffer from jaundice of hepatic origin
- F d. Maintain a normal body temperature in a cold environment
- F e. All.

Q. 05. **A premature infant is more likely than a full term infant to**
- T a. Excrete urine with a uniform specific gravity
- T b. Suffer from anaemia
- T c. Suffer from jaundice of hepatic origin
- F d. Maintain a normal body temperature in a cold environment
- F e. All.

Male reproductive system

Q. 06. **Primary sex organ of the male is**
- T a. testes
- F b. prostate
- F c. seminal vesicles.
- F d. penis
- F e. scrotum

Q. 07. **Cart wheel appearance of nucleus is seen in**
- T a. Sertoli cell
- F b. Leydig cell
- F c. Sperms
- F d. Spermatid
- F e. All.

Q. 08. **Testes does not produce**
- T a. Fructose
- F b. Estradiol
- F c. Testesterone
- F d. Inhibin
- F e. All.

Q. 09. **Testes can produce**
- T a. Estradiol
- T b. Testesterone
- T c. Inhibin
- F d. Fructose
- F e. All.

Q. 10. **For development of seminiferous tubules require**
- T a. androgens
- T b. FSH
- F c. LH
- F d. somatostatin
- F e. oxytocin.

Q. 11. **The seminal vesicles**
- T a. secrete fibrinogen.
- T b. provide fructose
- T c. secrete prostaglandins
- F d. increases motility of the sperm
- F e. provide clotting enzymes.

Q.12. **Prostaglandins found in the seminal fluid are the secreting products of**
- T a. Seminal vesicle
- F b. Prostate gland
- F c. Leydig cells
- F d. Sertoli cells.
- F e. All.

Q. 13. **The epididymis**
- T a. is the storage site for sprem.
- T b. increases motility of sperm
- T c. increases fertility of sperm
- F d. secretes alkaline fluid
- F e. secretes fibrinogen

Q. 14. **Prostate gland**
- T a. provides clotting enzymes.
- T b. secretes alkaline fluid
- F c. provides fructose
- F d. secretes prostaglandin
- F e. is the storage site for sperm

Q. 15. **The interstitial cells of the testes**
- T a. are stimulated by luteinizing hormone
- T b. secrete hormone testosterone
- F c. contribute to the volume of seminal fluid
- F d. secrete hormone inhibin
- F e. are under control of follicle stimulating hormone.

Q. 16. **Blood testis barrier is formed by**
- T a. Sertoli cells
- F b. Leydig cells
- F c. Epididymis
- F d. Vas deferens
- F e. All.

Q. 17. **Testicular function is regulated by the (action of)**
- T a. luteinizing hormone
- T b. gonadotropin releasing hormone
- T c. follicle stimulating hormone
- F d. human chorionic gonadotropin
- F e. prolactin.

Q. 18. **Precursor of testesterone is**
- T a. Pregnenalone
- F b. Methyl testeterone
- F c. Aldosterone
- F d. Cortison
- F e. All.

Q. 19. **Testosterone**
- T a. secretion is regulated by LH
- T b. causes descend of testes
- T c. causes the development of secondary sexual charac teristics in male.
- F d. is secreted by sertoli cells of testes
- F e. it is protein hormone

Q. 20. **Testosterone**
- T a. induces the DNA-RNA transcription process.
- T b. is formed by the leydig cells
- F c. is a large polypeptide
- F d. does not liberate from fetal testes
- F e. inhibits the descent of the testes

Q. 21. **Peak testosterone levels are seen at about**
- T a. 7-8 AM
- F b. 7-8 PM
- F c. 2 AM
- F d. 12 PM
- f e. 10 PM

Q. 22. **Testosterone is produced and secreted by**
- T a. interstitial cells of leydig
- F b. spermatogonia
- F c. sertoli cell
- F d. tubules
- F e. epididysis.

Q. 23. **Testosterone is formed from**
- T a. Cholesterole
- T b. Pregnenolone
- T c. Androstenedione
- T d. All.
- F e. None.

Q. 24. **Testosterone causes**
- T a. development of accessory organ
- T b. loss of hair during puberty
- T c. acne.
- F d. development of fetal brain
- F e. depletion of protein

Q. 25. **Following are the effects of teslostone**
- T a. Calcium retention
- T b. Increase total quantity of bone matrix
- T c. Increase BMR
- F d. Haemopoiesis
- F e. All.

Q. 26. **Following are the effects of teslostone except:**
- T a. Haemopoiesis
- F b. Calcium retention
- F c. Increase total quantity of bone matrix
- F d. Increase BMR
- F e. All.

Q. 27. **Anabolic action on protein is mediated by**
- T a. Testesterone
- F b. ACTH
- F c. Insulin

F d. TSH
F e. All.

Q. 28. **The acrosome contains**
T a. proteolytic enzyme
T b. hyaluronidase
F c. spermatocyte
F d. chromatin
F e. miochondria.

Q. 29. **Sperm becomes motile in the**
T a. epididymis
F b. urethra
F c. testes.
F d. seminiferous tubules
F e. vas deferens

Q. 30. **Human spermatozoa**
T a. contain 23 chromosomes
T b. have enzymes in their head (which aid penetration of the ovum)
F c. are motile in the seminiferous tubules
F d. are stored in the seminal vesicles
F e. are produced faster at 37°c.

Q. 31. **The sperms are normally motile at the rate of**
T a. 1-3 cm/min
F b. 0-1 cm/min
F c. 3-10 cm/min
F d. 10-15 cm/min
F e. 5-8 cm/min.

Q. 32. **In spermatogenesis**
T a. testosterone is essential for growth of sperm
T b. estrogen is essential for spermatogenesis
T c. GH necessary for metabolic function of testes.
F d. LH stimulates the sertoli cells
F e. FSH stmulates leyding cells

Q. 33. **Spermatogenesis**
T a. starts at the time of puberty.
T b. requires testosterone and LH
T c. requires 64-74 days
F d. occurs in epididymis
F e. requires high temperature

Q. 34. **Hormones that regulate spermatogenesis are**
T a. growth hormone
T b. testosterone
T c. follicle stimulating hormone
T d. estrogen
F e. aldosterone.

Q. 35. **Spermatozoa mature in which of the following organs**
T a. Epidydimis
F b. Vas-deferens
F c. Rete-testes
F d. Prostate
F e. All.

Q. 36. **Regarding semen**
T a. contains fructose, prostaglandin, citrate and phosphate.
T b. has milky appearance.
F c. volume is 5-10 ml/ejaculation
F d. pH is acidic
F e. it is mainly provided by fluid in the vasdeferens.

Q. 37. **A man may become infertile**
T a. if the spermatozoa are non motile
T b. if the testes remain in abdomen
T c. if suffered from mumps
T d. due to vasectomy.
F e. if spermatozoa is below 200 million/ml in semen.

Q. 38. **Nightmares are seen in**
T a. REM sleep
F b. NREM stage II
F c. NREM stage III
F d. NREM stage IV
F d. NREM stage V.

Q. 39. **In a male newborn the adrenogenital syndrome (con genital hyperplasia of the adrenal glands) is most often associate with**
T a. Normal appearing genitalia
F b. Hypoglycemia
F c. Pseudohermaphroditism
F d. Persistent paramesonephros (Mullerian ducts)
F e. All.

Female reproductive system

Q. 40. **In the female genital tract the spermatozoa do not live for more than**
T a. 48 hours
F b. 12 hours
F c. 24 hours
F d. 36 hours
F d. 72 hours

Q. 41. **Maximum growth spurt is seen in girls at time of**
T a. Pubarche
F b. Thelarche
F c. Menarche
F d. Adrenarche
F e. All.

Q. 42. **Normal body temperature can be raised by**
T a. Gonadotrophins

F b. Androgens
F c. Oestrogen
F d. Progesterone
F e. None.

Menstruation & ovulation

Q. 43. **In the endometrial cycle**
T a. menstruation occurs due to lack of estrogen and progesterone.
T b. there are prolifemtive, secretory and menstrual phase.
F c. proliferative phase is under the influence of progesterone.
F d. secretory phase is under the influence of estrogen.
F e. LH surge is required for menstruation.

Q. 44. **Elasticity of cervical mucous is seen at time of**
T a. Midcycle
F b. Proliferative
F c. Luteal stage
F d. Menstruation
F e. All.

Q. 45. **During follicular phase occurs the**
T a. develoment of antral follicle
T b. menstruation
T c. proliferation of endometrium
F d. secretion of progesterone
F e. reduced vascularization.

Q. 46. **During luteal phase, occurs the**
T a. glycogen storage in endometrium
T b. secretion of progesterone
T c. vascularization of endometrium
F d. proliferation of endometrium
F e. development of antral follicle.

Q. 47. **Ovulation**
T a. leads to begin secretion of progesterone
T b. needs diminishing estrogen secretion after prolonged phase excessive secretion to occur.
T c. needs LH to occur
F d. occurs during proliferative phase of the female sexual cycle
F e. usually occurs 28 days after the onset of menstruation.

Q. 48. **If a lady presents with a very regular 29 days menstrual cycle, ovulation should occur on day**
T a. 15
F b. 14
F c. 17
F d. 19
F e. 9

Q. 49. **Ovulation coincides with**
T a. LH surge
F b. Increase in progesterone
F c. GnRH release
F d. Increase in Oestrogen
F e. None.

Q. 50. **In ovarian cycle**
T a. ovulation does not occur by contraceptive pills
T b. there is normally discharge of single mature ovum in each ovarin cycle.
F c. follicular phase is under the control of estrogen
F d. luteal phase is under control of progesterone
F e. basal body temperature is decreased at the time of ovulation.

Q. 51. **An important facilitatory neurotransmitter mediating coitus induced ovulation is**
T a. Serotonin
F b. Dopamine
F c. Adrenalin
F d. Noradrenalaine
F e. None.

Q. 52. **Progesterone**
T a. prepares the uterus for implantation of the fertilized ovum
T b. causes development of decidual cells in the uterine endometrium
T c. is a steriod hormone
T d. promotes the development of the lobule and alveoli of the breast
F e. increases the uterine contraction during pregnancy.

Q. 53. **Progesterone is produced by**
T a. Granulosa luteal cells
F b. Theca cells
F c. Stroma of ovary
F d. Sertoli cells
F e. All.

Q. 54. **Estrogen**
T a. stimulates the growth of ductile system of breast
T b. causes Na^+ and water retention by the renal tubules.
T c. is formed from cholesterol
F d. acts by activating cAMP system
F e. is only secreted by the ovarian cells

Q. 55. **Estrogen acts on**
T a. Nuclear receptors
F b. Cellular membrane receptors
F c. Cytoplasmic receptors

F d. Mitochondrial receptors
F e. All.

Q. 56. **Estrogen acts on**
T a. Nucleus
F b. Mitochondria
F c. Cell membrane
F d. Cytoplosmic receptor
F e. None.

Q. 57. **Which is not caused by estrogen**
T a. Decreased folate levels
F b. Decreased HDL
F c. Increased blood sugar
F d. Decreased serum alkaline phosphatase
F e. All.

Q. 58. **The excretion of estrogens and progesterones are through**
T a. Urine
F b. Bite
F c. Sweat
F d. Feces
F e. All.

Q. 59. **Function of leutenizing hormone is**
T a. Follicle maturation and ovulation
F b. Milk secretion
F c. Causes progesterone secretion during ovulation
F d. Maintains placenta
F e. All.

Pregnancy, Labour & Lactation

Q. 60. **The viability of the spermatozoa within the female genital tract is upto ..... hrs.**
T a. 48
F b. 6
F c. 12
F d. 24
F e. 36.

Q. 61. **Fertilization of ovum occurs in the**
T a. ampulla of the uterine tube
F b. body of the uterine tube
F c. fundus of the uterus
F d. isthmas of the uterine tube
F è. abdominal cavity.

Q. 62. **Endocrine function of placenta is to secrete**
T a. prolactin
T b. human chorionic gonadotropin
T c. estrogen
T d. progesterone
F e. oxytocin

Q. 63. **In pregnancy**
T a. Plasma fibrinogen levels are increased
F b. Fibrinogen levels are decreased
F c. Thyroglobulins are decreased
F d. IgD are markedly increased
F e. All.

Q. 64. **Maternal changes system during pregnancy are increased**
T a. blood volume
T b. cardiac output to 30-40% above normal
T c. heart rate
F c. blood pressue
F e. white blood cell count.

Q. 65. **For the maintenance of pregnancy, progesterone**
T a. stimulates the growth of the endometriun
T b. prepares breast for milk production
T c. serves as precursor for estrogen synthesis
F d. causes contractions of the uterus
F e. inhibits the secretion from endometrial gland

Q. 66. **During pregnancy ovultion is ceassed due to**
T a. high levels of estrogen
T b. inhibition of the secretion of GnRH
T c. low levels of LH
F d. low levels of progesterone
F e. high levels of FSH.

Q. 67. **Maximum production of HCG occurs during**
T a. Third trimester
F b. First trimester
F c. Second trimester
F d. Implantation
F e. All.

Q. 68. **Human chorionic gonadotropic hormone**
T a. is a placental hormone
T b. promotes growth of corpus luteum.
T c. can be detected in the urine as an early sign of pregnancy
F d. is chemically steroid in nature
F e. acts on the uterus to maintain normal endometrium

Q. 69. **HCG (human chorionic gonadotropin)**
T a. acts on the ovaries to maintain corpusluteum
T b. can be detected in the urine.
F c. is secreted by hypothalamus
F d. is a steroid hormone
F e. concentration in the blood rises steadily through out the pregnancy

Q. 70. **Human chorionic somatomammotropin hormone**
T a. is a placental hormone
T b. causes deposition of protein

T c. has molecular weight of about 38000
T d. decreases insulin sensitivity and deecrea ses utilization of glucose in mother.
F e. is chemically steroid in nature

Q. 71. **The human chorionic gonadotropin prevents regeneration of**
T a. corpus luteum
T b. stimulates the corpus luteum
T c. stimulates steroid synthesis in fetus
F d inhibits testosterone production by fetal testes
F e. stimulates maternal lymphocyte production

Q. 72. **Hormone which does not cross placenta**
T a. Insulin
F b. Thyroxine
F c. Oestrogen
F d. None
F e. All.

Q. 73. **The uterine contraction of labour are stimulated by**
T c. oxytocin
T e. prostaglandin.
T d. relaxin
F a. estrogen
F b. progesterone

Q. 74. **Under stressful condition, secretion of**
T a. cortisol is increased
T b. growth hormone is increased.
F c. oxytocin is decreased
F d. erythropoietin is increased
F e. aldosterone is decreased

Q. 75. **Prolactin**
T a. concentration during pregnancy is 10-20 times higher than that of non preganant preiod
T b. is concerned with secretion of milk
F c. is secreted by ovary
F d. is concerned with ejection of milk
F e. secretion is regulated by anterior pituitary gland.

Q. 76. **Braxton-Hicks contractions**
T a. Occur during most of the months of pregnancy
F b. Is a positive feedback system
F c. Is another terms for labor contractions
F d. Result in hypoxia of the fetus
F e. All.

Q. 77. **Pregnant women who have had five or more previous babies differ from those who have had none in that they have a greater risk of**
T a. Developing anaemia
T b. Complications due to Rhesus incompatibility
T c. Malpresentation
T d. Involuntary passing of urine while coughing or laughing
T e. All of the above

Q. 78. **Oogonia are derived from**
T a. Yolk Sac
F b. Amnion
F c. Stroma of ovary
F d. Germinal epithelium
F e. All.

Q. 79. **The role of Human placental lactogen is**
T a. Growth of fetus
F b. Stimulate milk production
F c. Fetal breast development
F d. Endocrine regulation
F e. None

Q. 80. **Disseminated intravascular coagulation is seen in**
T a. Retained placenta
F b. Hemophilia
F c. Thrombocytopenia
F d. None
F e. All.

Q. 81. **Temporary methods of contraception are**
T a. oral pill
T b. intrauterine contraceptive device (IUCD)
T c. condom
F d. vasectomy
F e. tubectomy.

Menopause

Q. 82. **Regarding menopause**
T a. it occurs at the ages of 45-55 years of life
T b. large quantities of FSH and LH are produced after menopause
T c. reproductive function of females is lost after menopause.
T d. it occurs due to burning out of ovaries
F e. concentration of estrogen is increased after menopause

Q. 83. **Menopause is characterizied by**
T a. diminished female sex hormones concentration
T b. continuous secretion of large amount of follicle stimulating hormone
T c. hot flushes.
F d. temporary amenorrhea
F e. onset of first menstruation

Q. 84. **Menopausal hormonal relations are**
T a. Gonadotropins increase estrogens decrease

F b. LH/TSH increase
F c. Estrogens and gonadotropins decrease
F d. Both increase.
F e. All.

Q. 85. **Levels of which of the following hormones are increased in post menopauusal women**

T a. FSH
F b. Estrogen
F c. Progesterone
F d. Cortisone
F e. All.

Q. 86. **Menopausal hot flushes is due to**

T a. LH Surge
F b. Decreased estroge
F c. Decreased progesteron
F d. FSH Surge
F e. None

Q. 87. **Estrogen in the post menopausal women is metabolised mostly into**

T a. Estrone
F b. Estriol
F c. Estradiol
F d. Androstenedione
F e. All.

10
Digestive System

Introduction

The gastrointestinal system is the portal through which nutritive substances, vitamins, minerals, and fluids enter the body. Proteins, fats, and complex carbohydrates are broken down into absorbable units ***(digested)***, principally in the small intestine. The products of digestion and the vitamins, minerals, and water cross the mucosa and enter the lymph or the blood ***(absorption)***.

Digestion of the major foodstuffs is an orderly process involving the action of a large number of digestive enzymes.
Enzymes from the :

1. *Salivary and lingual glands* attack carbohydrates and fats.
2. *Enzymes from the stomach* attack proteins and fats.
3. *Enzymes from the exocrine portion* of the pancreas attack carbohydrates, proteins, lipids, DNA and RNA.
4. Other *enzymes that complete the digestive process are found in the luminal membranes and the cytoplasm* of the cells that line the small intestine.

The action of the enzymes is aided by the hydrochloric acid secreted by the stomach and the bile secreted by the liver.

The mucosal cells in the small intestine are called ***enterocytes***. In the small intestine they have a ***brush border*** made up of numerous microvilli lining their apical surface. This border is rich in enzymes. It is lined on its luminal side by a layer that is rich in neutral and amino sugars, the ***glycocalyx***. The membranes of the mucosal cells contain glycoprotein enzymes that hydrolyze carbohydrates and peptides and the glycocalyx is made up in part of the carbohydrate portions of these glycoproteins that extend into the intestinal lumen. Next to the brush border and glycocalyx is an ***unstirred layer*** similar to the layer adjacent to other biologic membranes. Solutes must diffuse across this layer to reach the mucosal cells. The mucous coat overlying the cells also constitutes a significant barrier to diffusion.

Substances pass from the lumen of the gastrointestinal tract to the interstitial fluid and thence to the lymph and blood by-

i. diffusion, ii. facilitated diffusion, iii. osmosis, iv. solvent drag, v. active transport, vi. secondary active transport (coupled transport), and vii. endocytosis.

Most substances must pass from the intestinal lumen into the mucosal cells (enterocytes) and then out of the enterocytes to the interstitial fluid, and the processes responsible for movement across the luminal cell membrane are often quite different from those responsible for movement across the basal and lateral cell membranes to the interstitial fluid.

(Ref. Ganong 22th edition, Page 447)

Digestion

Difinition: Digestion may be defined as a physiological process by which complex food particles are broken down into simple form, suitable for absorption and subsequent utilization.

Purpose of digestion

i. Supply energy to the body for activity.
ii. For the growth of the body.
iii. For the repair of wear and tear.
iv. For the reproduction and lactation.

Parts of digestive system

i. Mouth or buccal cavity with tongue
ii. Oropharynx
iii. Oesophagous
iv. Stomach.
v. *Small intestine :*
   a. Duodenum
   b. Jejunum and ileum
vi. *Large intestine:*
   a. Caecum
   b. Ascending colon
   c. Transverse colon
   d. Descending colon
   e. Sigmoid colon
   f. Rectum
   g. Anal canal.

Accessory parts of digestive system :

i. Teeth
ii. Salivary glands : Parotid, submandibular, sublingual
iii. Liver
iv. Pancreas
v. Gall bladder
vi. Other digestive glands in the wall of the digestive tract.

Alimentary tract : Extend from mouth to anus with their associated glands.

Gastrointestinal tract (GIT) : Extend from stomach to anus.

Table 10-4. Mean lengths of various segments of the gastro intestinal tract as measured by intubation in living humans.

Pharynx, esophagus, and stomach	65 cm
Duodenum	25 cm
Jejunum and ileum	260 cm
(Ref. Ganong 22th Edition) Colon	110 cm

Table 10-1 : **Local hormones with their source, cause of secretion and functions :**

Name	*Source*	*Cause of secretion*	*Site of action*	*Function*
1. Gastrin.	Antral mucosa of stomach.	Presence of food in stomach.	Stomach, lower oesophageal sphincter, small intestine, G. bladder.	1. Stimulates gastric acid & pepsin secretion. 2. Increases stomach motility. 3. Contracts lower oesophageal sphincter.
2. Secretin.	Duodenal mucosa. ductal cell.	Presence of acidic chyme into duodenum.	Pancrease Stomach	1. Increases hydrolytic type of pancreatic secretion. 2. Decreases gastric secretion of acid.
3. Cholecys-tokinine.	Mucosa of upper small intestine.	Presence of fatty substance, protein in duodenum.	Gall bladder.	1. Increases bile secretion. 2. Contraction of G. bladder. 3. Contraction of sphincter of oddi.
4. Pancreo zymine.	Mucosa of upper small intestine.	Presence of fatty substance, protein in duodenum.	Pancreas.	1. Ecbolic type of pancreatic secretion. 2. Decreases stomach Motility.
5. Gastric inhibitory peptide (G.I.P)	Mucosa of duodenum and jejunum.	Presence of fat and glucose in duodenum.	Stomach.	1. Inhibits gastric secretion & motility. 2. Stimulate intestinal secretion of water & electrolytes.
6. Vaso-active intestinal peptide (VIP)	Mucosa of duodenum and jejunum.	Presence of chyme in the intestine.	Intestine	1. Stimulates intestinal secretion of water and electrolytes.
7. Villikinin.	Intestine.	Presence of chyme in the intestine.	Villi	1. Increases the motility of villi. 2. Constriction of blood vessel.
8. Enterocrinin	Mucosa of upper S. intestine.	Presence of chyme in the intestine.	Intestine	1. Increases intestinal secretion.
9. Entero gastrone.	Duodenal mucosa.	Presence of fat in duodenum.	Stomach mucosa.	1. Inhibit gastric secretion.
10. Motiline.	Duodenal mucosa.	Presence of fat in duodenum.	Stomach mucosa.	1. Stimulates gastric motility & intestinal juice secretion.
11. Bombesin.	GIT mucosa.	Immunoreactivity.	Small intestine.	1. Increase gastric secretion 2. Increase motility of small intestine and gall bladder.

Others :

12. Somatostatin
13. Neurotensin
14. Substance P
15. Serotonin; glucagon
16. Opoid peptides
17. GRP gastrinreleasing peptide.

Table 10-2 : **Principal digestive enzymes. The corresponding proenzymes are shown in parentheses.**

Source	Enzyme	Activator	Substrate	Catalytic Function or Products
Salivary glands	Salivary alpha amylase	Cl^-	Starch	Hydrolyzes 1 : 4α Act linkages, producing α-limit dextrins, maltotriose, and maltose
Lingual glands	Lingual lipase	-	Triglycerides	Fatty acids plus 1 ,2-diacylglycerols
Stomach	Pepsins (pepsinogens)	HCI	Proteins and polypeptides	Cleave peptide bonds adjacent to aromatic amino acids
	Gastric lipase	-	Triglycerides	Fatty acids and glycerol
Exocrine pancreas	Trypsin (trypsinogen)	Enteropep-tidase	Proteins and polypeptides	Cleave peptide bonds on carboxyl side of basic amino acids (arginine or lysine)
	Chymotrypsins (chymo-trypsinogens)	Trypsin	Proteins and polypeptides	Cleaves peptide bonds on carboxyl side of aromatic amino acids
	Elastase (proelastase)	Trypsin	Elastin, some other proteins	Cleaves bonds on carboxyl side of aliphatic amino
	Carboxypeptidase A (pro-carboxypeptidase A)	Trypsin	Proteins and polypeptides	Cleaves carboxyl terminal amino acids that have aromatic or branched aliphatic side chains
	Carboxypeptidase B (pro-carboxypeptidase B)	Trypsin	Proteins and polypeptides	Cleaves carboxyl terminal amino acids that have basic side chains
	Colipase (procolipase)	Trypsin	Fat droplets	Facilitates exposure of active site of pancreatic lipase
	Pancreatic lipase	...	Triglycerides	Monoglycerides and fatty acids
	Cholesteryl ester hydrolase	...	Cholesteryl esters	Cholesterol
	Pancreatic alpha-arnylase	Cl^-	Starch	Same as salivary alpha amylase
	Ribonuclease	...	RNA	Nucleotides
	Deoxyriibonuclease	...	DNA	Nucleotides
	Phospholipase A_2 (prophospholipase A_2)	Trypsin	Phospholipids	Fatty acids, lysophospholipids
Intestinal mucosa	Enteropeptidases	...	Trypsinogen	Trypsin
	Aminopeptidases	...	Polypeptides	Cleave amino terminal amino acid from peptide
	Carboxypeptidases	...	Polypeptides	Cleave carboxyl terminal amino acid from peptide
	Endopeptidases	...	Polypeptides	Cleave between residues in midportion of peptide
	Dipeptidases	...	Dipeptides	Two amino acids
	Maltase	...	Maltose, maltotriose, alpha-dextrins	Glucose
	Lactase	...	Lactose	Galactose and glucose
	Sucrase[1]	...	Sucrose: also malto-triose and maltose	Fructose and glucose
	alpha Dextrinase[1]	...	alpha-Dextrins, maltose, maltotriose	Glucose
	Trehalase	...	Trehalose	Glucose
	Noclease and related enzymes	...	Nucleic acids	Pentoses and purine and pyrimidine bases
Cytoplasm of mucosal cell	Various peptidases	...	Di-, Tri-, and tetrapeptides	Amino acids

[1] *Sucrase and alpha-dextrinase are separate subunits ot a single protein.*

(Ref. Ganong 22th Edition, Page 468, 469)

Function of digestive tract

1. Ingestion of food.
2. Digestion of food.
3. Secretion of various digestive juice.
4. Absorption of H_2O, vitamines, salt and end products of digestion.
5. Excretion of heavy metals, toxins etc.
6. Helps in movement of food through it.
7. Regulation of acid base balance.
8. Regulation of water balance.
9. Regulation of blood sugar level.
10. Helps in erythropoiesis.

Function of the different parts of GIT

Functions of oral cavity

1. It is the receiving chanel of the food staff.
2. It helps in breaking down the food staff into small fragments by mastication (Chewing).
3. It helps formation of bolus, by mixing the ground up food staff with saliva.
4. By formation of bolus, it helps swallowing.
5. It elps in conveying the sensation of taste of the food, by the test buds of tongue.
6. Some amount of salivary digestion may also occur in the buccal cavity.

Function of Stomach

1. *Mechanical function :*
   a. Stomach acts as reservior of food.
   b. The movement of the stomach helps in proper mixing of food with disgestive juice and also helps to propel the food into the duodenum.
2. *Digestive function :* Due to the presence of pepsin, stomach digests protein upto the stage of peptone. It also digest fats to a some extent with the help of gastric lipase. Gastric renin coagulates milk, HcI causes some hydrolysis of food staffs.
3. *Secretory function :* Stomach secretes gastric juice hormones like gastrin etc.
4. *Absorptive function :* Stomach absorbs small quantity of water, saliva, alcohol, glucose, certain drugs, vitamin B_{12} etc.
5. *Stimulatory function :* Stomach manufactures two chemical substances like hormone which are as follows :
   a. Gastrin : It acts as a stimulator for gastric juice secretion.
   b. Castle's intinsic factor : It is an enzyme like substances present in the gastric juice as well as in the gastric mucous membrane.

   The extrinsic factor is vit B_{12}. When it is taken in the mouth, the Castle's intrinsic factor interacts with extrinsic factor and helps in the absorption of Vit-B_{12}.

Function of large intestine (Colon)

1. *Absorptive function :* It helps in absorption of
   a. Water : 80% of H_2O.
   b. Salt : NaCI along with water.
   c. Sugar : Only glucose.
   d. Aminoacid : If amino acid escape absorption in the small intestine.
   e. Alcohol.
   f. Drug : Hypotonic drugs such as 5% paraldehyde, also sedative such as 40% magsulph.
   g. Anaesthetic agent.
   h. Steroid.
2. *Secretory function :* The chief secretion is mucus. Some amount of inorganic salts (chlorides) and HCO_3 along with some organic materials are also secreted.
3. *Excretory function :* Some heavy metals- Lead, bismuth, mercury and arsenic etc are excreted through the colon.
4. *Synthetic function :* Vit-K_1,Vit-K_2 and Vit B_{12}, folic acid etc are synthesized by the bacterial flora in the large intestine.
5. *Digestive function :* Large intestine is aboundant with bacterial flora. These bacterial flora helps in digestion.
6. *Expulsive or propulsive function :* Due to its mass peristaltic movement, it helps in the act of defecation.

***Integrated action of gastrointestinal hormones** in regulating digestion and utilization of absorbed nutrients.*

(The dashed arrow indicate inhibition.

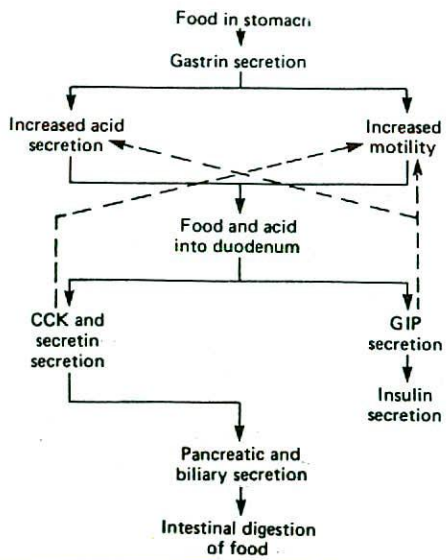


Table 10-3 : Integrated action of gastrointestinal hormones in regulating digestion & utilization of absorbed nutrients.

(Ref. Ganong 22th edition; Page-487)

Mucus

Mucus is a thick secretion composed mainly of water, electrolytes, and a mixture of several glycoproteins, which themselves are composed of large polysaccharides bound with much smaller quantities of protein.

Importance of mucus in the GIT :

1. It adhere tightly to the food or other particles and also to spread as a thin film over the surfaces.
2. It coats the wall of the gut and prevents actual contact of food particles with the mucosa.
3. Mucus has a low resistance to slipage so that the particles can slide along the epithelium with great ease.
4. Mucus causes fecal particles to adhere to each other to form the fecal masses.
5. Mucus is strongly resistant to digestion by the gastro-intestinal enzymes.
6. The glycoproteins of mucus have amphoretic properties and capable of buffering small amount of either acids or alkalies. Mucus also contains moderate amount of bicarbonate ions, which specifically neutralize acids.

(Ref. Guyton & Hall-11th Edition, Page 793)

Secretory functions of alimentary tract

Digestive juices

1. Saliva
2. Gastric juice
3. Pancreatic juice
4. Intestinal juice or succus intericus
5. Bile.

Daily secretion of intestinal juices :

Juice	*Daily Volume (ml)*	*PH*
Saliva	1000	6.0 - 7.0
Gastric secretion	*1500*	*1.0 - 3.5*
Pancreatic secretion	1000	8.0 - 8.3
Bile	*1000*	*7.8*
Small intestinal secretion	1800	7.5 - 8.0
Brunner's gland secretion	*200*	*8.0 - 8.9*
Large intestinal secretion	200	7.5 - 8.0
Total	*6700*	-

(Ref. Guyton & Hall-11th Edition, Page 794)

Q. **Why different digestive juice are necessary for digestion of food?**

Ans. Different digestive juices are necessary for digestion of food because-

i. One particular digestive juice does not contain all enzymes necessary for digestion of food staffs. e.g saliva contain only carbohydrate splitting enzyme.

ii. One particular digestive juice cannot even digest particular food upto its completion. E.g. Gastric juice digest protein upto the stage of peptone, pancreatic juice digest peptone upto the stage of peptide, peptide then completely digested upto amino acids by the succus intericus.

iii. Reaction of different digestive juice are different.

For this reasons, different digestive juice are required for digestion of food.

Saliva

Salivary glands

Salivary glands are mixed gland. There are mainly three pairs of salivary glands- parotid, submaxillary or submandibular and sublingul glands. In addition, there are many small buccal glands.

a. ***Parotid glands :*** Parotid glands secret entirely the serous type, containing ptyelin (an alpha-amylase). The gland opens upon the inner surface of the cheek opposite the second upper molar tooth, by a single duct called the duct of Stensen.

b. ***Submaxillary or submandibular glands :*** Secret both the serous type and mucous. The gland open upon the floor of the mouth on the side of the frenulum of the tongue, by Wharton's duct.

c. ***Sublingul gland :*** Secret both the serous types and mucous. The gland open by several fine ducts, upon the floor of the mouth by the side of the frenulum. These are called the ducts of Rivinus.

d. ***Buccal glands*** : There are small accessory buccal glands scattered throughout the mucous membrane and secret only mucous.

(Ref. Guyton & Hall-11th Edition, Page 793, 794)

Table 10-5. ***Characteristics of each pair of salivary glands in human*** :

Gland	*Parasympathetic nerve supply via*	*Histologic type*	*secretion*	*% ot*
Parotid	Glossopharyngeal	Serous	Watery	25%
Subman-dibular	Facial	Mucous & serous	Moderately viscus	70%
Sublingul	Facial	Mucous & serous	Viscus	05%

(Ref. Ganong 22th edition, Page 488)

Control of salivary secretion

Salivary secretion is under neural control.

1. *Parasympathetic nerve* : Stimulation of the parasym pathetic nerve supply causes profuse secretion of watery saliva with a relatively low content of organic material. Associated with this secretion is a pronounced vasodilation in the gland, which appears to be due to the local release of VIP. This polypeptide is a cotransmitter with acetylcholine in some of the postganglionic parasympathetic neurons. Atropine and other cholinergic blocking agents reduce salivary secretion.

2. *Sympathetic nerve* : Stimulation of the sympathetic nerve supply causes vasoconstriction and, in humans, secretion of small amounts of saliva rich in organic constituents from the submandibular glands.

Food in the mouth causes reflex secretion of saliva. and so does stimulation of the vagal afferent fibers at the gastric end of the esophagus. Salivary secretion is easily conditioned. In humans, the sight, smell, and even thought of food causes salivary secretion ("makes the mouth water").

(Ref. Ganong 22th edition, Page 489)

Q. **Salivation cannot be a process of excretion, it is chiefly a secretory process- *Explain*.**

Ans. Following observations prove that salivation is mainly a secretory phenomenon :

1. Saliva is extremly useful, hence, caot be an excretory product.
2. Evidence of work : During salivation the glands are found to be actively working.
   a. During salivation the glands inerease in size, become vascular and their temperature increases.
   b. Hydrostatic pressure in the salivary duct increases.
   c. The osmotic pressure. becomes higher than that of blood.
   d. The amount of oxygen used and CO_2 produced by the gland increase.
   e. Saliva contain certain substances, not present in blood e.g ptyalin.
3. The zymogen and mucinogen granules which are present in resting glandular cells, reduce to a much smaller number during activity.
4. Changes of electric potential takes place in the gland during secretion.

Saliva

Definition : Saliva is a viscus, colourless, oplacent fluid which is secreted by the three pairs of salivary glands- the parotid, submandibular, and sublingual glands. There are also many small buccal glands from which salivation occurs.

Characters :

1.	Total secretion	:	800 - 1500ml/day.
	Average	:	1000 ml/day.
2.	Reaction	:	Slightly acidic
3.	pH	:	6.0 - 7.0
4.	Specific gravity	:	1.002 - 1.012.

(Ref. Guyton & Hall-11th Edition, Page 793)

N.B. pH : 7.0-8.0; Total secretion : about 1500 ml. *(Ganong 20th,P-473)*

Composition of saliva :

A. Water : 99.5%

B. Solid : 0.5%
   i. *Organic* : 0.3%
      a. Enzyme : Ptyaline (salivary alpha-amylase), Lingual lipase, Carbonic anhydrase phosphatase, Lysozymes.
      b. Other organics : Mucin, urea, cholesterol, amino acids.
      c. Blood group substances : Antigen of ABO blood group.
   ii. *Inorganic* (0.2 %) : NaCl, KCl, acid and alkaline sodium phosphate, calcium phosphate, $CaCO_3$, $KHCO_3$ etc.
   iiii. *Cellular constituents :* Yeast cell, bacteria, protozoa etc.
   iv. *Gases :* O_2, N_2, CO_2.

(Ref. Ganong 22th edition, Page-489; Guyton & Hall-11th P-793 & Others)

Function of saliva

1. *Mechanical functions :*
   i. It keps the mouth moist and helps in speech
   ii. It facilates swallowing
   iii. It helps in preparing food staffs into a bolus, suitable for digestion
   iv. It dilutes hot and irritent food, thus prevents injury of the mucous membrane
   v. Saliva also acts as a lubricant
   vi. It washes down the food debris there by prevent bacterial growth.
2. *Helps in taste :* By dissolving food staffs saliva helps in taking the sensation of taste.
3. *Disgestive function :* It breaks down boil starch into maltose due to the presence of enzyme ptyalin.

   eg. Boiled starch $\xrightarrow{ptyalin}$ Erythrodextrin $\xrightarrow{ptyalin}$ Achrodextrin $\xrightarrow{ptyalin}$ Maltose.

4. *Excretory function :* It excrets urea, some heavy metals (Pb, Bi, As, etc.), thyocyanates, certain drugs like iodine, alkaloids such as morphine; antibiotics such as penicilin etc.
5. *Helps in water balance :* Saliva keeps the mouth moist, when moisture is reduced in the mouth, certain nerve ending at the back of the tongue are stimulated and the desire of thirst arises. The subject then take water and thus water balance is maintained.
6. *Buffering function :* Due to the presence of HCo_3^- and Po_4 in saliva it acts as bufter-$NOHCO_3$, H_2CO_3 and Na_2HPO_4, NaH_2PO_4.
7. *Bacteriolytic action :* Cell membrane of different varities

of bacteria contains polysaccharides, lysosome. The enzymes present in the saliva is a polysaccharide, thus it dissolves the cell wall of many bacteria and finally kills them.

Q. ***Why ptyalin can not act on unboiled starch?***

Ans. Ptyalin can not act on unboiled starch because it cannot penetrate the protective membrane of unboiled starch.

Mechanism of saliva secretion *(/Regulation)* :

Saliva secretion is purely a reflex processes. Two types of reflex are :

a. *Condition reflex (acquired reflex) :* Here salivation occurs in presence of food such as sight, vision & smell of food stimulate saliva secretion reflexly although no food is actually given in mouth.

b. *Unconditioned or inherent or inborn reflex :* When food is actually given to the mouth then the secretion of salivary gland occurs by uncondition reflex.

Salivation also occur in response to reflexes originating in the stomach and upper intestines-particularly when very irritating foods are swallowed or when a person is nauseated because of some gastro-intestinal abnormality.

When a person smells or eats favourite food salivation is greater than when disliked food is smelled or eaten.

(Ref. Guyton & Hall-11th Edition & others)

Test for saliva

Collected saliva is taken into 4 test tube labelled with I, II, III, & IV.

1. A little unboiled starch is taken in a tubes no- I and I cc of saliva added to it → Iodine test → No change in colour → *Salivary amylase do not acts upon unboiled starch.*
2. A little boiled starch is taken in test tube no-II and I cc of saliva is added with it → Iodine test → Gradually the colour changes to purple red → *Salivary amylase acts upon boiled starch & hydrolyzed it.*
3. A little boiled starch taken in test tube no-III and I cc of boiled saliva is added to it → Iodine test → No change in colour → *Saliva is destroyed during boiling.*
4. A little HCI is taken in tube no-IV & I cc of saliva is added to it → Iodine test → No change of colour → *Saliva has no action on HCI.*

Applied :

Achalasia : It is a condition in which food accumulates in the esophagus and the organ becomes massively dilated.

Causes : It is due to increased resting lower oesophageal sphincter (LES) tone and incomplete relaxation upon swallowing. The myenteric plexus of the esophagus is deficient at the LES in this condition, and there is defective release of NO and VIP.

Treatment : It can be treated by pneumatic dilation of the sphincter or incision of the esophageal muscle (myotomy). Inhibition of acetylcholine release by injection of botulinum toxin into the LES is also effective and produces relief that lasts for several months.

(Ref. Ganong 22th edition, Page-490)

Gastroesophageal reflux disease : It is a condition of LES incompetence, which permits reflux of acid gastric contents into the esophagus. This common condition causes heartburn and esophagitis and can lead to ulceration and stricture of the esophagus due to scarring. In severe cases, there is weakness of the intrinsic sphincter, the extrinsic sphincter or both, but less severe cases are caused by intermittent periods of poorly understood decreases in the neural drive to both sphincters. The condition can be treated by inhibition of acid secretion with H_2 receptor blockers or omeprazole. Surgical treatment in which a portion of the fundus of the stomach is wrapped arround the lower esophagus so that the LES is inside a short tunnel of stomach is also effective.

(Ref. Ganong 22th edition, Page-490)

Aerophagia & Intestinal Gas : Nervous persons who hyperventilate sometimes swallow large amounts of air, and some air is unavoidably swallowed in the process of eating and dinking (***aerophagia***). Some of the swallowed air is regurgitated (***belching***), and some of the gases it contains are absorbed, but much of it passes on to the colon. Here, some of the oxygen is absorbed, and hydrogen, hydrogen sulfide, carbon dioxide, and methane formed by the colonic bacteria from carbohydrates and other substances are added to it. It is then expelled as ***flatus***. The smell is largely due to sulfides. The volume of gas normally found in the human gastrointestinal tract is about 200 ml, and the daily production is 500-1500 ml. In some individuals, gas in the intestines causes cramps, ***borborygmi*** (rumblng noises), and abdominal discomfort.

(Ref. Ganong 22th edition, Page-491)

Aptyalism : Aptyalism or Xerostomia is a condition of complete cessation of salivary secretion.

Causes :

i. Congenital Hypoplasia
ii. Abscence of salivary gland
iii. When mouth is dry
iv. Chewing is difficult
v. Speech is trouble some.

Temporary cessation occurs in Anxiety, worry, fear, shock,

Hyposalivation : Reduced salivation (less than normal) is called hyposalivation.

Cause :

i. Deep X-ray rodiation given to salivary gland.
ii. Surgical intervention.

Hypersalivation : Excessive salivation (more than normal) is called hypersalivation. It is also called *ptyalism or sialorrhoea.*

Causes :

i. During pregnancy.
ii. Ulcer tongue & mouth.
iii. Neoplasm of tongue, buccal cavity & oesophagus.
iv. Carious tooth or deformed tooth.
v. Gastric or Duodenal ulcer with pancreatic inflammation.
vi. Parkinsonism & psychoneurosis.

Sialolithiasis : Stone (calculi) in the salivary duct is called sialolithiasis.

Esophagial Secretion

The esophageal secretions are entirely mucoid in character and principally provide lubrication for swallowing. The main body of the esophagus is lined with many simple mucous glands, at the gastric end and to a lesser extent in the initial portion of the esophagus, there are many compound mucous glands. The mucus secreted by the compound glands in the upper esophagus prevents mucosal excoriation by newly entering food, whereas the compound glands located near the esophagogastric junction protect the esophageal wall from digestion by acidic gastric juices that often reflux from the stomach back into the lower esophagus. Despite this protection, a peptic ulcer at times may occur at the gastric end of the esophagus.

(Ref. Guyton & Hall-11th Edition, Page 795)

Gastric Secretion

Gastric glands with their secretion

There are three types of gland present in the stomach :

1. *Cardiac gland :* It contains mainly mucous secreting cells.
2. *Glands of body and fundus of stomach (Gastric glands or oxyntic glands)* : These glands are located on the inside surfaces of the body and fundus of the stomach, constituting the proximal 80% of the stomach.
   a. *Mucous neck cell :* Secrete mainly mucus but also some pepsinogen.
   b. *Peptic or chief or zymogenic cell :* Secrete large quantities of pepsinogen, gastric renin.
   c. *Oxyntic or parietal cell :* Secrete HCl and intrinsic factor of Castle.
   d. *Enterochromaffin cell :* Secrete gastrin and serotonin.
3. *Pyloric glands :* Mucus neck cell : secrete mucin & hormone gastrin. These glands are located in the antral portion of the stomach, constituting the distal 20% of the stomach.

(Ref. Guyton & Hall-11th Edition, Page 795 and others)

Intrinsic factor of castle : It is an enzyme like unidentified substance secreted by the stomach, sugested by Castle, called intinsic factor of castle. It is essential for the absorption of vitamin B_{12}.

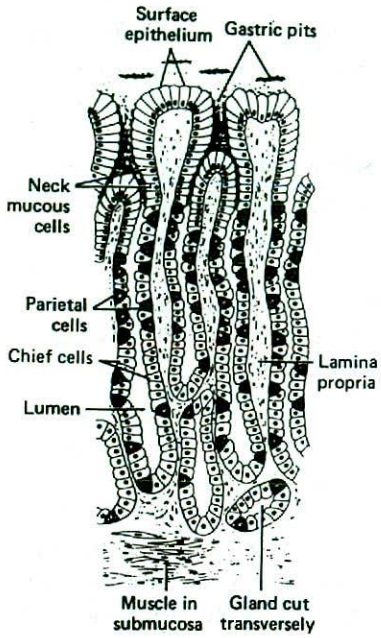


Fig. 10-1. *Diagram of glands in the mucosa of stomach.*

Characteristics of gastric juice :

1. *Quantity* : 500 - 1000 ml/meal
   or 1200-2500 ml/day
   or 1500 ml/day *(Guyton 11th)*
   or 2500 ml/day *(Ganong 22th, P-491)*
2. *Consistancy* : Cloudy and sticky due to presence of mucin and cells.
3. *Reaction* : Strongly acidic; P^H : 1.0 - 3.5
4. *Specific gravity* : 1.002-1.004.

(Ref. Ganong 22th Edition, Page 491, 492 & Others)

Composition of gastric juice :

A. *Water* : 99.5%
B. *Solid* : 0.5%
   a. *Inorganic :*
      i. Cations : Na^+, K^+, Mg^{++}, H^+
      ii. Anions : Cl^-, HPO_4^{2-}, SO_4^{2-},
      iii. HCl, $CaCl_2$, $Ca_3(PO_4)_2$
   b. *Organic :*
      i. Enzyme : Pepsins (Pepsinogens), gastric lipase.
      ii. Mucin.
      iii. Intrinsic factor of Castle.
      iv. Blood group substances : Antigen of ABO blood group found in gastric juice during stomach cancer.

(Ref. Ganong 22th edition, Page-492 & Others)

Function of gastric juice

1. *Digestive function :*
   a. The enzyme *pepsinogen* with the help of gastric HCI digests *protein* upto the stage of *peptone*.
   b. *Renin* coagulates casinogen of *milk* and converts it into *casein* and then into insoluble *calcium caseinate*.
   c. *Gastric lipase* digests fat to some extent.
2. *Excretory function :* Toxins, heavy metals, certain alkaloids etc are excreted through gastric juice.
3. *Function of HCl of Gastric juice :*
   a. Gastric HCl converts inactive pepsinogen into active pepsin.
   b. Gastric HCl acts as an antiseptic agent against bacteria.
   c. Gastric HCl causes hydrolysis of all the food staffs.
   d. It keeps iron in ferrous state for absorption.
   e. In presence of gastric HCl pepsinogen digest protein upto the stage of peptone.
   f. It provides suitable environment for the action of enzymes pepsin, renin & lipase.
   g. It helps in maintaining a proper environment for gastric emptying.
   h. It converts collagen protein into gelatin.
   i. It hydrolyzes cane sugar to glucose & fructose.
   j. It helps in the dissolution of the protoplasmic covering of the fat globules.
4. Antiseptic function : Gastric HCl acts an antiseptic agent against bacteria.
5. Haemopoietic function : The intrinsic factor of gastric juice helps absorption of extrinsic factor (Vit-B_{12}) essential for maturation of RBC.
6. Lubricating function : The mucin of gastric juice lubricates any irritant, which might have gained entry into the stomach.
7. Protective function : The mucin is responsible for protecting the gastric mucosa from the action of HCI. Thus stomach is not self digested.
8. Acid base regulation : It is responsible for the alkaline tide of blood, during secretion of HCl.

Secretion and activation of pepsinogen

Pepsinogen is secreted by the peptic and mucous cells of the gastric glands. When the pepsinogen is first secreted, they have no digestive activity. However, as soon as they come in contact with the hydrochloric acid and specially when they come in contact with previously formed pepsin and hydro chloric acid, they are immediately activated to form active pepsin.

In this process, the pepsinogen molecule, having a molecular weight of about 42,500 is split to form pepsin. Pepsin is an active proteolytic enzyme, molecular weight of about 35,000. Optimum pH 1.8 to 3.5, but above a pH of about 5 it has almost no proteolytic activity and even becomes completely inactivated in a short time.

(Ref. Guyton & Hall-11th Edition, Page 797)

Basic mechanism of secretion of gastric HCl

The *parietal (oxyntic)* cells contain a system of intracellular canaliculi. The hydrochloric acid is formed at the membranes of these canaliculi and then conducted through openings to the exterior. Mechanism of HCI secretion is consists of the following steps :

1. Chloride ion is actively transported from the cytoplasm of the parietal cell into the lumen of the canaliculus, and sodium ions are actively transported out of the lumen. These two effects together create a negative potential of -40 to -70 millivolts in the canaliculus, which inturn causes passive diffusion of positively charged potassium ions and a small number of sodium ions from the cell cytoplasm also into the canaliculus. Thus, in effect, mainly potassium chloride and much smaller amounts of sodium chloride enter the canaliculus.

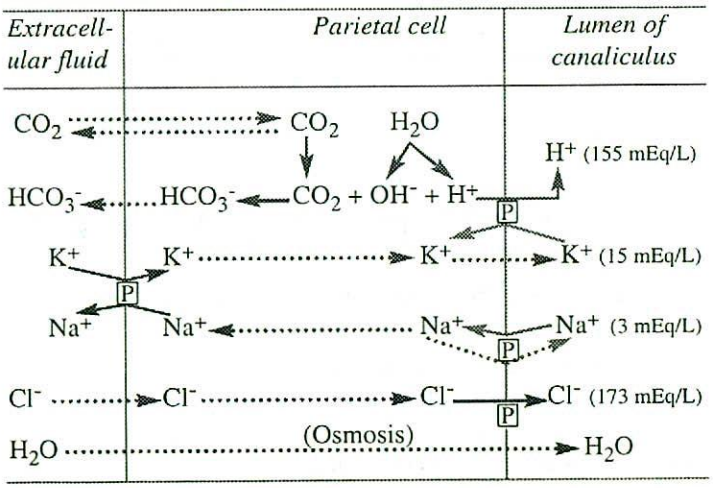


Fig.10-2. *HCl secretion by parietal cells in the stomach. Source: Guyton 10th.*

2. Water becomes dissociated into hydrogen ions and hydroxyl ions in the cell cytoplasm. The hydrogen ion is then actively secreted into the canaliculus in exchange for potassium ions, catalyzed by H^+-K^+ ATPase. In addition, the sodium ions are actively reabsorbed by a seperate sodium pump. Thus, most of the potassium and sodium ions that had diffused into the canaliculus are reabsorbed into the cell cytoplasm, and hydrogen ions take their place in the canaliculus, giving a strong solution of hydrochloric acid in the canaliculus, which is then secreted outward through the open end of the canaliculus into the lumen of the gland.
3. Water passes into the canaliculus by osmosis because of the secretion of the ions into the canaliculus. Thus, the final secretion from the canaliculus contains approximately hydrochloric acid at a concentration of 150 to 160 mEq/L, potassium chloride at a concentration of 15 mEq/L, and a small amount of sodium chloride.

4. Finally, carbon dioxide, either formed during metabolism in the cell or entering the cell from the blood, combines under the influence of carbonic anhydrase with the hydroxyl ions (formed in step 2 when water was dissociated) to form bicarbonate ions. This then diffuses out of the cell cytoplasm into the extracellular fluid in exchange for chloride ions that enter the cell from the extracellular fluid and are later secreted into the canaliculus.

(Ref. Guyton & Hall-11th Edition, Page 796)

Q. **For peptic digestion HCl is must- explain.**

Ans. For peptic digestion HCl is must because :

1. HCl of gastric juice converts inactive pepsinogen into active pepsin, by loss of about 15% of the nitrogen content of the pepsinogen molecule.
2. Pepsin is inactive in neutral or alkaline medium but it is highly proteolytic in strong acid solutions.

Q. **Lack of peptic activity causes poor meat digestion- Explain.**

Ans. Meat contain protein. Proteins are absorbed in the form of amino acids, so proteins are digested to amino acid prior to their absorption.

1. Pepsin is the proteolytic enzyme, which helps in protein digestion.
2. It converts 10 -15% protein to amino acid.
3. With the help of HCl; pepsin converts protein upto the stage of peptone.

   Protein → Acid metaprotein → Primary proteoses → Secondary proteoses → Peptone → Amino acid.

   As meat is protein, in the absence of proteolytic (peptic) activity meat is poorly digested.

Regulation of gastric secretion

Gastric motility and secretion are regulated by neural and humoral mechanisms. The neural components are local autonomic reflexes, involving cholinergic neurons, and impulses from the CNS by way of the vagus nerves. The humoral components are gastrin, enterogastrone.

Vagal stimulation increases gastrin secretion by release of gastrin-releasing peptide. Other vagal fibers release acetylcholine, which acts directly on the cells in the glands in the body and the fundus to increase acid and pepsin secretion. Stimulation of the vagus nerve in the chest or neck increases acid and pepsin secretion but vagotomy does not abolish the secretory response to local stimuli.

For convenience, the physiologic regulation of gastric secretion is usually discussed in terms of *cephalic, gastric, and intestinal influences, although these overlap*. The *cephalic influences* are vagally mediated responses induced by activity in the CNS. The *gastric influences* are primarily local reflex responses and responses to gastrin. The *intestinal influences* are the reflex and hormonal feedback effects on gastric secretion initiated from the mucosa of the small intestine.

(Ref. Ganong 22th edition, Page-494)

Phases of gastric secretion

Gastric secretion is said to occur in three phases : a cephalic phase, a gastric phase, and an intestinal phase. As will be apparent in the following discussion, these three phases fuse together.

i. ***Cephalic phase*** : The cephalic phase of gastric secretion occurs even before food enters the stomach, especially while it is being eaten. It results from the sight, smell, thought or taste of food, and the greater the appetite, the more intense is the stimulation. Neurogenic signals that cause the cephalic phase of gastric secretion can originate in the cerebral cortex or in the appetite centers of the amygdala or hypothalamus. They are transmitted through the dorsal motor nuclei of the vagi and thence through the vagus nerves to the stomach. This phase of secretion normally accounts for about *20 per cent of the gastric secretion* associated with eating a meal.

ii. ***Gastric phase*** : Once food enters the stomach, it excites- i. long vagovagal reflexes, ii. local enteric reflexes, and iii. the gastrin mechanism, all of which in turn cause secretion of gastric juice during several hours while the food remains in the stomach.

   The gastric phase of secretion accounts for about *70 per cent of the total gastric secretion* associated with eating a meal and therefore accounts for most of the total daily gastric secretion of about 1500 milliliters.

iii. ***Intestinal phase*** : The presence of food in the upper portion

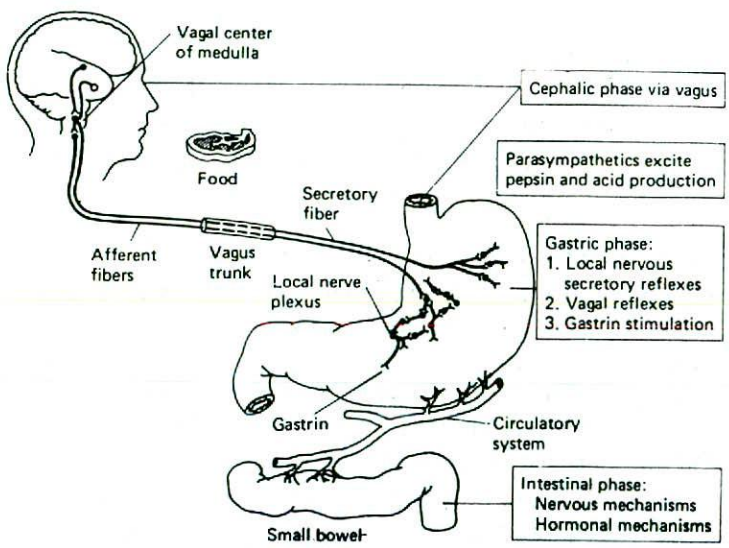


Fig. 10-3. Phase of gastric secretion & their regulation

of the small intestine, particularly in the duodenum, will continue to cause the stomach to secrete small amounts of gastric juice, probably partly because of small amounts of gastrin that are released by the duodenal mucosa in response to distention or partly because of chemical stimuli of the same type as those that also stimulate the stomach gastrin mechanism.

(Ref. Guyton & Hall-11th Edition, Page798)

Appetite juice *(Cephalic phass of gastric juice secretion)*

Cephalic phass of gastric juice secretion is refered to as appetite juice by Pavlov.

i. *Characteristics of cephalic phase of gastric juice secretion* :
   1. It is rich in HcI and pepsinogen and copious in amount.
   2. It is abolished by cutting the vagus nerves or by administration of blocking agents.
   3. It has two reflex elements : Both conditioned and uncondition reflexes.
   4. Hunger profoundly influences the secretion.
   5. Food, agreeably flavoured, attractive in appearance also helps in the secretion of the juice.
   6. Congenial surroundings and friendly company in the dining table also helps in this phase.
   7. Disagreable food, disgusting appearance and foul odor, all depress it.

ii. *Importance of cephalic phase of gastric juice secretion* :
   1. The acidity of the juice maintain the acid media and PH of the stomach & destroy the foreign particles comes with food particles.
   2. The acidity converts the pepsinogen into active pepsin and maintain a suitable environment for the action of pepsin.
   3. Pepsin of the juice begins to hydrolysis of protein food particles.
   4. It helps to initiate the second phase of gastric secretion.

Factors affecting gastric secretion

1. *Emotions :*
   a. Pleasant surroundings, elevated mood increase secretion.
   b. Unpleasant surroundings, fear, grief, shock depress it.
2. *Food :*
   a. Palatable food stimulates secretion.
   b. Disagreeable food depress it.
3. *Drink :* Pre-lunch drinks (alcoholic) stimulate gastric secretion.
4. *Alkalies :*
   a. In large doses - depress secretion.
   b. In small doses- stimulates secretion.
5. *Biters :* Unless the bitters contain alcohol, they have hardly any effect on gastric secretion.
6. *Acids :* HCI (1%) depress secretion when directly put inside the stomach.
7. *Drugs :* Like Histamine, Histalog, Caffine & alcohol and Insulin stimulate gastric secretion.
8. Tobacco smoking : Stimulate secretion.
9. *Vitamins :* Deficiency of Vit-B_{12} & Vit B_1 depress gastic secretion and respectively causes- Achylia gastrica and achlorhydria. Administration of Vit-D sometimes depress secretion.
10. *Electrolytes :* Changed blood calcium level depress secretion.
11. Hormones :
    a. ACTH, Steroid and Gastrin increase secretion.
    b. Serotonine, Enterogastrone depress it.

Factors increasing gastric juice secretion

Certain factors inhibits acid sceretion. These are :

i. Distension of the stomach.
ii. Sight, smell, taste of food.
iii. Low blood sugar level through hypothalamus.
iv. Gastrin.
v. *Insulin* : By lowering blood sugar level.
vi. *Cortisol* : Increase gastric secretion which is rich in acid pepsin but poor in mucin.

Factors inhibits gastric HCl secretion

Certain factors inhibits acid sceretion. These are :

i. Emotion, fear, grief and sensation of nausea.
ii. The presence of fat in the duodenum.
iii. High levels of (H^+) in the pyloric antrum or proximal duodenum.
iv. The presence of hyperosmolar concentration in the duodenum.

Alkaline tide

After a heavy meal, the HCI secretion will increase which also increases the production of HCO_3^-. This HCO_3^- then enters in the plasma and increases the pH of blood. As a result, alkalinity occurs, known as alkaline tide.

Post parandal alkaline tide

At the sametime, the alkalinity of urine will also be increased. All these condition are called post parandal alkaline tide.

Important constitent of gastric juice

i. Pepsin
ii. Gastric HCI
iii. Casle's intrinsic factor.
iv. Mucin.

Stimuli that affect gastrin secretion

i. *Stimuli that increase gastrin secretion.*
   1. *Luminal* :

a. Peptides and amino acids
b. Distention

2. *Neural* : Increased vagal discharge via GRP
3. *Blood borne* : Calcium, Epinephrine.

ii. *Stimuli that inhibit gastrin secretion*

1. *Luminal* :
   Acid
   Somatostatin
2. *Blood borne* : Secretin, GIP, VIP, glucagon, calcitonin.

(Ref. Ganong 22th edition, Page-485)

Q. **Why normal gastric juice secretion is essential for erythropoiesis?**

Ans. Extrinsic haemopoietic factor vit. B_{12} is essential for maturation of RBC and its deficiency leads to pernicious anaemia. One of the constituents of gastric juice, *intrinsic factor of Castle's* helps in absortption of vit-B_{12} which is released from the pyloric mucosa. Gastric mucosal atrophy, partial or total gastectomy or gastoejunostomy may leads to decreased gastric intrinsic factor secretion which causes pernicious anaemia. So, gastric secretion is essential for erythropoiesis.

Q. **Stomach does not digest itself- *Explain***

Ans. Stomach does not digest itself because :

1. Gastric mucosal glands of the stomach secret mucus which form a protective gastric mucosal barrier. For this barrier HCl and pepsin does not come in contact with the mucous membrane of the stomach.
2. Greater HCO_3^- ion concentration of blood flowing through gastric mucosa to counter act effect of HCl.
3. Presence of Antipepsin to counteract peptic digestion.
4. Production of NH_3 by urease locally, another doubtful neutralizer of HCl.

So stomach does not digest itself.

(Ref. Ganong 22th edition, Page-491 & others)

Applied :

Achylia Gastrica : It is a condition in which neither any HCl nor any pepsin is found in gastric juice. It is found in about 2-5% of normal individual.

This is a congenital error due to non-development of oxyntic and peptic cells. This condition dose not affect health, because pancreatic enzymes can digest all the ingested food staffs.

Hypochlorhydria : In certain pathological condition (pernicious anaemia; cancer of the stomach etc) the acidity of the gastric juice is very low, called hypochlorhydria.

Achlorhydria : When the acidity of the gastric juice is absent.

Hyperchlorhydria : Some people may have higher acidity in the gastric juice, called hyperchlorhydria.

Peptic Ulcer

a. *Definition* : Ulceration of any part of GIT due to action of excessive acid pepsin secretion.

b. *Cause of peptic ulcer* :

i. Excess acid and pepsin secretion by gastic mucosa.
ii. Irritation.
iii. Poor blood supply.
iv. Poor secretion of mucus.
v. Diminished capability of the gastro duodenal mucosal barrier to protect against the digestive properties of the acid-pepsin complex.

c. *Treatment of peptic ulcer :*

i. *Medical treatment :*

1. Reduction of stressful situations that might lead to excessive acid secretion.
2. Administration of antacid drugs and cimitidine or Ranitidine.
3. Interdiction of smoking
4. Removal of such ulcer causing factors as alcohol, aspirin, etc.

ii. *Surgical treatment :*

1. Vagotomy.
2. Removal of portion of stomach.

(Ref. Guyton & Hall-11th Edition, Page 820)

Ryles tube

It is a thin flexible rubber tube, of small bore, 12 french gauge (8mm) with an expanding perforated end and enclosing a metal bead (Ryle) is used for swallowing it into the stomach, other end is open.

i. *Markings* : It has three markings.
When swallowed up :

a. First marking coincides with incisor teeth (about 30 cm or 12 inches from the end), the end is near the cardiac end of oesophagus :
b. If upto the second mark, the end is within the stomach.
c. When upto the third mark, the end has entered the duodenum.

ii. *Uses of Ryles tube :*

a. Gastric juice analysis.
b. Gastric juice aspiration.
c. Nasogastric feeding.
d. As torniquet.

Gastric juice analysis

Method of gastric juice analysis :

1. Functional gastric analysis or Functional test meal method by ryles tube.
2. Histamin tests of gastric secretion.
3. Insulin test of gastric secretion.

Functional test meal method : It is the commonly used method for gastric juice analysis.

a. *Procedure :* The subject is kept in fasting condition since previous evening. In the morning, during gastric analysis, the subject is swallows the tube upto the second mark. The fasting contents of the stomach is withdrawn completely, by a syringe and preserved.

Then 10ml of samples are drawn every 15 minutes for analysis after half an hour of swallowing a pint of thin gruel, which acts as test meal for stimulating gastric secretion. This drawing of samples goes on for 2.5 hours.

The samples including resting stomach contents are then tested for:

1. Free acidity (HCI).
2. Combined acidity.
3. Total acidity.
4. Total chloride.
5. Starch and sugar.
6. Bile.
7. Blood.
8. Lactic acid.
9. Mucous & resence of pepsin.

b. *Importance :* This test not only gives an idea of the secreting capacity of stomach but the degree ofmotility, opening time of pylorus & duodenal regurgitation.

Pancreatic juice

Characteristics of pancreatic juice

1. *Quantity* : 800-1500 ml/day, average 1500ml/day.
2. *Consistancy* : Colourless, odorless and low viscosity.
3. *Reaction* : Strongly alkaline, P^H: 8.0 (Ganong 20th)
4. *Specific gravity* : 1.010-1.030.

(Ref. Ganong 22th edition, Page 497 & others)

Composition of pancreatic juice

A. Water : 98.5%

B. Solid : 1.5%.

a. *Organic :*

Enzymes : Pancreatic secretion contains enzymes for digesting all three major types of food : proteins, carbohydrates, and fats.

i. *Proteolytic* : *Trypsin* (Trypsinogen), *chymotrypsin* (chymotrypsinogen), *carboxypolypeptidase* (procarboxypolypeptidase), elastase (proelas tases), and nucleasea- ribonucleas (RNA ase), deoxyribo nuclease (DNA ase).

ii. *Carbohydrate splitting enzyme* : Pancreatic alpha amylase, which hydrolyzes starches, glycogen, and most other carbohydrates (except cellulose) to form disaccharides and a few trisaccharides.

iii. *Fat spliting enzyme* : Pancreatic lipase, colipase (procolipase), cholesterol enterase and phospholipase A_2 (phospholipase A_2).

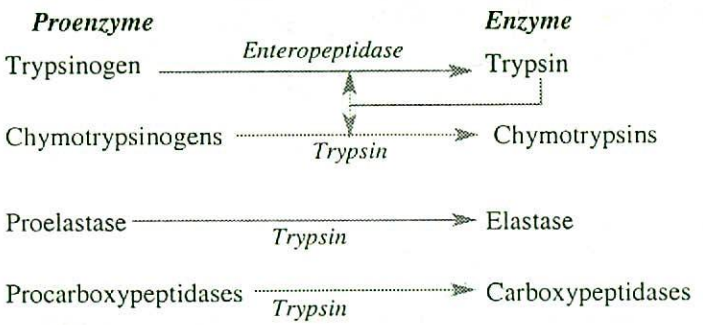
b. *Inorganic* :

i. Cations : Na^+, K^+, Ca^{++}, Mg^{++}.

ii. Anions : Large quantity of HCO_3^- (approximately 113 meq/L; *in plasma it is about 24 meq/L*), Cl^-, SO_4^{2-}, HPO_4^{2-}.

(Ref. Ganong 22th edition, Page 497; Guyton & Hall-11th Edition, Page 799 & others)

Activation of the pancretic proteases in the duodenal lumen



(Ref. Ganong 22th edition, Page 498)

Functions of pancereatic juice

A. ***Digestive action*** : Due to the presence of high concentration of different enzymes, pancreatic juice digest all three types of food- proteins, carborhydrates and fats.

1. *Proteolytic activity :* Proteoses, peptones and polypeptides are coverted into polypeptides and amino acids by the action of trypsin, chymotrypsin, carboxypolypeptidase and proteases.

RNA ase and DNA ase split two types of nuclic acid (RNA and DNA) into nucleo tides.

2. *Amylolytic activity :* Pancreatic amylase acts both on boiled and unboiled starch, glycogen and most other carbohydrates except cellulose to form disaccharides (maltose, isomaltose, multotriose) and few trisaccharides.

3. *Lipolytic activity :* Pancreatic lipase hydrolyzes neutral fat into fatty acids and monoglycerides; Cholesterol esterase hydrolyzes cholesterol esters; Phospholipase splits fatty acids from phospholipids with the help of some factor as - a. bile salt, b. alkaline media, in which pancreatic lipase acts best.

B. ***Neutralizing action*** : Pancreatic juice contains large quantities of HCO_3^-, which plays an important role in neutralizing the acid chyme emptied by the stomach into the duodenum.

(Ref. Guyton & Hall-11th Edition, Page799)

Trypsin inhibitor

(Why pancreas does not digested by its own proteolytic enzymes?)

Ans. Secretion of trypsin inhibitor prevents digestion of the pancreas itself. It is important that the proteolytic enzymes of the pancreatic juice not become activated until after they have been secreted into the intestine because the trypsin and other enzymes would digest the pancreas itself. Fortunately, the same cells that secrete the proteolytic enzymes into the acini of the pancreas secrete simultaneously another substance called trypsin inhibitor. This substance is formed in the cytoplasm of the glandular cells, and it prevents activation of trypsin both inside the secretory cells and in the acini and ducts of the pancreas. Because it is trypsin that activates the other pancreatic proteolytic enzymes, trypsin inhibitor prevents the subsequent activation of the others as well.

When the pancreas becomes severely damaged or when a duct becomes blocked, large quantities of pancreatic secretion sometimes become pooled in the damaged areas of the pancreas. Under these conditions, the effect of trypsin inhibitor is sometimes overwhelmed, in which ease the pancreatic secretions rapidly become activated and can literally digest the entire pancreas within a few hours, giving rise to the condition called *acute pancreatitis*. This often is lethal because of accompanying circulatory shock; even if not lethal, it usually leads to a subsequent lifetime of pancreatic insufficiency.

(Ref. Guyton & Hall-11th Edition, Page800)

Secretion of bicarbonate ions (HCO_3^-)

Although the enzymes of the pancreatic juice are secreted entirely by the acini of the pancreatic glands, the other two important components of pancreatic juice, bicarbonate ions and water, are secreted mainly by the epithelial cells of the ductules and ducts that lead from the acini. The stimulatory mechanisms for enzyme production and production of bicarbonate ions and water are also quite different. When the pancreas is stimulated to secrete copious quantities of pancreatic juice, the bicarbonate ion concentration can rise to as high as 145 mEq/L, a value about five times that of bicarbonate ions in the plasma. This provides a large quantity of alkali in the pancreatic juice that serves to neutralize the hydrochloric acid emptied into the duodenum from the stomach.

The basic steps in the cellular mechanism for secreting sodium bicarbonate solution into the pancreatic ductules and ducts are the following :

1. Carbon dioxide diffuses to the interior of the cell from the blood and combines with water under the influence of carbonic anhydrase to form carbonic acid (H_2CO_3). The carbonic acid in turn dissociates into bicarbonate ions and hydrogen ions (HCO_3^- and H^+).

   Then the bicarbonate ions are actively transported in association with sodium ions (Na^+) through the luminal border of the cell into the lumen of the duct.

2. The hydrogen ions formed by dissociation of carbonic acid inside the cell are exchanged for sodium ions through the *blood* border of the cell by a secondary active transport process. This supplies the sodium ions (Na^+) that are transported through the luminal border into the pancreatic duct lumen to provide electrical neutrality for the secreted bicarbonate ions.
3. The movement of sodium and bicarbonate ions from the blood into the duct lumen creates an osmotic gradient that causes osmosis of water also into the pancreatic duct, thus forming an almost completely isosmotic bicarbonate solution.

(Ref. Guyton & Hall-11th Edition, Page800)

Regulation of the secretion of pancreatic juice

Three basic stimuli are important in causing pancreatic secretion :

1. *Secretin* : Secretion of pancreatic juice is primarily under hormonal control. Secretin acts on the pancreatic ducts to cause copious secretion of a very alkaline pancreatic juice that is rich in HCO_3^- and poor in enzymes. The effect on duct cells is due to an increase in intracellular cAMP. Secretin also stimulates bile secretion.
2. *Pancreozymine* : It acts on the acinar cells to cause the release of zymogen granules and production of pancreatic juice rich in enzymes but low in volume, its effect is mediated by phospholipase C.
3. *Acetylcholine* : It acts on acinar cells via phospholipase C to cause discharge of zymogen granules, and stimulation of vagi causes secretion of a small amount of pancreatic juice rich in enzymes. There is evidence for vagally mediated conditioned reflex secretion of pancreatic juice in response to the sight or smell of food.

Note that as the volume of pancreatic secretion increases, its Cl^- concentration falls and its HCO_3^- concentration increases. Although HCO_3^- is secreted in the small ducts, it is reabsorbed in the large ducts in exchange for Cl^-. The magnitude of the exchange is inversely proportionate to the rate of flow.

The epithelium of the small pancreatic ducts contains many CFTRs. The relation of CFTRs to HCO_3^- secretion is unsettled, but in cystic fibrosis, the HCO_3^- content and the volume of pancreatic juice are reduced and there is an increased incidence of chronic pancreatitis.

(Ref. Ganong 22th edition, Page 498)

Phases of pancreatic secretion

Pancreatic secretion occurs in three phases, the same as for gastric secretion : the cephalic phase, the gastric phase, and the intestinal phase. Their characteristics are as follows :

1. ***Cephalic phases*** : During the cephalic phase of pancreatic secretion, the same nervous signals that cause secretion in the stomach also cause acetylcholine release by the vagal

nerve endings in the pancreas. This causes moderate amounts of enzymes to be secreted into the pancreatic acini and ducts, accounting for about 20 per cent of the total secretion of pancreatic enzymes after a meal. Little of the secretion flows immediately out the pancreatic ducts into the intestine because only small amounts of water and electrolytes are secreted along with the enzymes.

2. ***Gastric phase*** : During the gastric phase, the nervous stimulation of enzyme secretion continues, accounting for another 5 to 10 per cent of the enzymes secreted after a meal. Still only small amounts reach the duodenum because of continued lack of significant quantities of fluid secretion.
3. ***Intestinal phase*** : After chyme enters the small intestine, pancreatic secretion becomes copious, mainly in response to the hormone secretin. In addition, cholecystokinin causes still more increase in the secretion of enzymes.
   a. ***Secretin stimulates secretion of copious quantities of bicarbonate- neutralization of the acidic stomach chyme*** : Secretin is present in an inactive form, prosecretin, in so-called *S cells* in the mucosa of the duodenum and jejunum. The secretin mechanism is especially important for two reasons :

   First, secretin begins to be released from the mucosa of the small intestine when the pH of the duodenal contents falls below 4.5 to 5, and its release increases greatly as the pH falls to 3.0. This immediately causes copious quantities of pancreatic juice containing abundant amounts of sodium bicarbonate to be secreted. The net result is then the following reaction in the contents of the duodenum :

   $$HCl + NaHCO_3 \longrightarrow NaCl + H_2CO_3$$

   Then the carbonic acid immediately dissociates into carbon dioxide and water. The carbon dioxide is absorbed into the blood and expired through the lungs, thus leaving a neutral solution of sodium chloride in the duodenum. In this way the acid contents emptied into the duodenum from the stomach become neutralized, and further peptic activity by the gastric juices in the duodenum is immediately blocked. Because the mucosa of the small intestine cannot withstand the digestive action of acid gastric juice, this is an essential protective mechanism to prevent development of duodenal ulcers.

   Second. bicarbonate ion secretion by the pancreas also provides an appropriate pH for action of the pancreatic enzymes, which function optimally in a slightly alkaline or neutral medium, at a pH of 7.0 to 8.0. Fortunately, the pH of the sodium bicarbonate secretion averages 8.0.

   b. ***Cholecystokinin- control of digestive enzyme secretion by the pancreas*** : The presence of food in the upper small intestine also causes a second hormone cholecystokinin, to be released from *I cells*, in the mucosa of the duodenum and upper jejunum. This release of cholecystokinin results especially from the presence of *proteoses* and peptones (which are products of partial protein digestion and of long-chain *fatty acids; h*ydrochloric acid from the stomach juices also causes its release in smaller quantities.

   Cholecystokinin causes mainly secretion of large quantities of digestive enzymes by the acinar cells. This effect is similar to that of vagal stimulation but even more pronounced, accounting for 70 to 80 per cent of the total secretion of the pancreatic digestive enzymes after a meal.

(Ref. Guyton & Hall-11th Edition, Page 801)

Hydrolytic type of secretion : When the acid-chyme enters in the duodenum causes the release of secretin by its mucosa which then passes through blood and enters pancreas and stimulate it to release pancreatic juice rich in HCO_3^- and water but poor in enzyme. This is called "*hydrolytic type*" of secretion.

(Ref. Guyton & Hall-11th Edition)

Ecbolic type of secretion : Entering of fatty food in the duodenum causes release of PZ-CCK by its mucosa which then passes through blood and enters in the pancreas and stimulate it to release pancreatic juice rich in enzyme but poor in HCO_3^-. This is called *"ecbolic type"* of secretion.

(Ref. Guyton & Hall-11th Edition)

Diference between hydrolytic and Ecbolic type of secretion

Hydrolytic	*Ecbolic*
1. Poor in enzyme but rich in HCO_3^-	1. Rich in enzyme but poor in HCO_3^-
2. It is thin and watery.	2. It is thick.
3. It is secreted by secretin.	3. It is secreted by PZ-CCK.
4. It is secreted in response to acid chyme in the duodenum.	4. It is secreted in response to fatty food in duodenum.
5. It mainly neutralizes the pH of chyme.	5. It is disgetive in function.

Secretions of the small intestine

Brunner's gland : In the duodenum there are small, coiled acinotubular duodenal glands called Brunner's glands.

Crypts of Lieberkhan : Throughout the small intestine there are simple tubular intestinal glands called crypts of Lieberkuhn.

Valvulae conniventes : These are valve-like folds in the mucous membrane in the small intestine. These are various kinds of enteroendocrine cells.

Paneth cells : Endocrine cells located in the depths of the crypts of Lieberkuhn-secrete defensins, naturally occurring peptide antibiotics that are also secreted elsewhere in the body. The migrating enterocytes are exposed to a high concentrate of the defenses, and this may protect them as they move to the tops of the villi. Paneth cells may also secret guanylin.

(Ref. Ganong 22th Edition; page-505, 506)

Secretions of the small intestine

1. ***Secretion of mucus by Brunner's glands in the duodenum*** : An extensive array of compound mucous glands, called *Brunner's glands*, is located in the first few centimeters of the duodenum, mainly between the pylorus and the papilla of Vater where the pancreatic juices and bile empty into the duodenum.

   a. *Secretions of these glands* : These glands secrete large amounts of alkaline mucus in response to- i. *tactile stimuli or irritating stimuli* of the overlying mucosa, ii. *vagal stimulation*, which causes increased Brunner's glands secretion concurrently with increase in stomach secretion; and iii. gastrointestinal hormones, especially *secretin*.

   b. *Function of the mucus secreted by Brunner's glands* :
      i. It protect the duodenal wall from digestion by the highly acid gastric juice.
      ii. The mucus contains a large excess of bicarbonate ions, which add to the bicarbonate ions from pancreatic secretion and liver bile in neutralizing the hydrochloric acid entering the duodenum from the stomach.

   c. *Sympathetic stimulation* : Brunner's glands are inhibited by sympathetic stimulation : therefore, such stimulation is likely to leave the duodenal bulb unprotected and is perhaps one of the factors that cause this area of the gastrointestinal tract to be the site of peptic ulcers in about 50 per cent of ulcer patients.

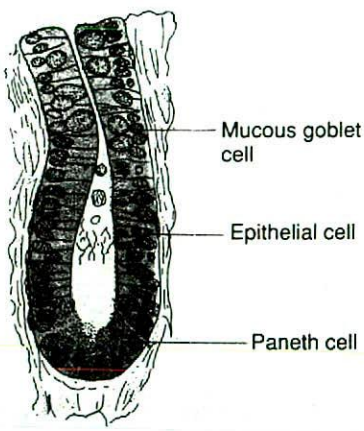


Figure10-6. *Crypt of Lieberkuhn, found in all parts of the small intestine between the villi, which secretes almost pure extracellular fluid.*

2. ***Secretion of the intestinal digestive juices by the Crypts of Lieberkuhn*** : Located over the entire surface of the small intestine are small pits called *crypts of Lieberkuhn*. These crypts lie between th intestinal villi. The intestinal surfaces of both the crypts and the villi are covered by an epithelium cornposed of two types of cells-

   a. a moderate number of *goblet cells*, which secrete mucus that lubricates and protects the intestinal surfaces.

   b. a large number of *enterocytes*, which, in the crypts secrete large quantities of water and electrolytes and, over the surfaces of the villi, reabsorb the water and electrolytes along with the end products of digestion.

The intestinal secretions are formed by the enterocytes of the crypts at a rate of about 1800 ml/day.

The secretions are almost pure cxtracellular fluid and have a slightly alkaline pH in the range of 7.5 to 8.0.

The secretions also are rapidly reabsorbed by the villi. This circulation of fluid from the crypts to the villi supplies a watery vehicle for absorption of substances from the chyme as it comes in contact with the villi. Thus, the primary function of the small intestine is to absorb the nutrients and their digestive products into the blood.

(Ref. Guyton & Hall-11th Edition, Page 805)

Mechanism of secretion of the watery fluid : The exact mechanism that causes the marked secretion of watery fluid by the crypts of Lieberkuhn is not known. It is believed to involve at least two active secretory processes : i. active secretion of chloride ions into the crypts and ii. active secretion of bicarbonate ions. The secretion of these ions causes electrical drag of sodium ions through the membrane and into the secreted fluid as well. Finally, all these ions together cause osmotic movement of water.

(Ref. Guyton & Hall-11th Edition, Page 805)

Digestive enzymes in the small intestinal secretion

When secretions of the small intestine are collected without cellular debris, they have almost no enzymes. However, the *enterocytes of the mucosa*, especially those that cover the villi, do contain digestive enzymes that digest specific food substances while they are being absorbed through the epithelium.

These enzymes are the following :

i. Several peptidases for splitting small peptides into amino acids i.e enteropeptidase, aminopeptidases, carboxypeptidases, endopeptidases, dipeptidases

ii. Four enzymes for splitting disaccharides into monosaccharides - sucrose, maltose. isomaltase, and lactase.

iii. Small amounts of *intestinal lipase* for splitting neutral fats into glycerol and fatty acids.

Most if not all of these digestive enzymes are located mainly in the *brush border of the enterocytes*. They are believed to

catalyze hydrolysis of the foods on the outside surfaces of the microvilli before absorption of the end products.

The epithelial cells deep in the crypts of Lieberkflhn continually undergo mitosis, and the new cells migrate along the basement membrane upward out of the crypts toward the tips of the villi, thus continually replacing the villus epithelium. As the villus cells age, they are finally shed into the intestinal secretions. The *life cycle of an intestinal epithelial cell is about 5 days.* This rapid growth of new cells also allows rapid repair of excoriations that occur in the mucosa.

(Ref. Guyton & Hall-11th Edition, Page 805)

Regulation of Small Intestinal Secretion

1. *Local stimuli* : By far the most important means for regulating small intestinal secretion are various local nervous reflexes, especially reflexes initiated by tactile or irritative stimuli and by the increase in enteric nervous activity associate with the gastrointestinal movements. Therefore, for the most part, secretion in the small intestine occurs simply in response to the presence of chyme in the intestine- the greater the amount of chyme, the greater the secretion.
2. *Hormonal regulation* : Some of the same hormones that promote secretion elsewhere in the gastrointestinal tract also increase small intestinal secretion, especially secretin and cholecystokinin. Also, some experiments suggest that other hormonal substances extracted from the small intestinal mucosa by the chyme might help to control secretion. In general, the local enteric reflex mehanisms almost certainly play by far the dominant role.

(Ref. Guyton & Hall-11th Edition, Page 806)

Enteropeptidase

i. *Source* : This enzyme is secreted by the brush border when the pancreatic juice enters the duodenum.

ii. *Content* : Enteropeptidase contains 41% polysaccharide, and this high polysaccharide content apparently prevents it from being digested itself before it can exert its effect.

iii. *Function* : The powerful protein-splitting enzymes of the pancreatic juice are secreted as inactive proenzymes. Trypsinogen is converted to the active enzyme trypsin by the enzyme enteropeptidase (enterokinase) when the pancreatic juice enters the duodenum.

Substrate : Trypsinogen

Product : Trypsin.

iv. *Deficiency symptoms* : Enteropeptidase deficiency occurs as a congenital abnormality and leads to *protein malnutrition.*

(Ref. Ganong 22th Edition; page 497)

(Q. 10. Write short notes on- Enteropeptidase)

Secretions of the large intestine

Large intestinal secretions are :

1. ***Mucus Secretion*** : The mucosa of the large intestine, like that of the small intestine, has many crypts of Lieberkuhn, but in this mucosa, unlike that of the small intestine, there are no villi. Also, the epithelial cells contain almost no enzymes. Instead, they consist mainly of mucous cells that secrete only mucus.

   Therefore, the great preponderance of secretion in the large intestine is mucus. This mucus contains large amounts of bicarbonate ions caused by active transport through other epithelial cells that lie between the mucus-secreting epithelial cells.

   Function of mucus : Mucus in the large intestine protects the wall against excoriation, but in addition, it provides the adherent medium for holding fecal matter together. Furthermore, it protects the intestinal wall from the great amount of bacterial activity that takes place inside the feces, and it plus the alkalinity of the secretion (pH of 8.0 caused by large amounts of sodium bicarbonate) provides a barrier to keep acids formed deep in the feces from attacking the intestinal wall.

   Regulation of secretion of mucus : The rate of secretion of mucus is regulated principally by direct, tactile stimulation of the mucous cells on the surface of the mucosa and by local nervous reflexes to the mucous cells in the crypts of Lieberkuhn. Stimulation of the pelvic nerves, which carry the parasympathetic innnervation to the distal one half to two thirds of the large intestine, also causes marked increase in the secretion of mucus. This occurs alnong with an increase in motility. Therefore, during extreme parasympathetic stimulation, often caused by emotional disturbances, so much mucus may be secreted into the large intestine that the person has a bowel movement of ropy mucus as often as every 30minutes; this mucus contains little or no fecal material.

2. ***Secretion of water and electrolytes in response to irritation*** : Whenever a segment of the large intestine becomes intensely irritated, as occurs when bacterial infection becomes rampant during enteritis, the mucosa secretes large quantities of water and electrolytes in addition to the normal viscid solution of alkaline mucus. This acts to dilute the irritating factors and to cause rapid movement of the feces toward the anus. The usual result is diarrhea, with loss of large quanitites of water and electrolytes. But the diarrhea also washes away the irritant factor, which promotes earlier recovery from the disease than would otherwise occur.

(Ref. Guyton & Hall-11th Edition, Page 806)

Liver and Biliary System

Principal functions of the liver

1. *Formation and secretion of bile*
2. *Nutrient and vitamin metabolism :*
   - Glucose and other sugars
   - Amino acids
   - Lipids
     - Fatty acids
     - Cholesterol
     - Lipoproteins
   - Fat soluble vitamins
   - Water soluble vitamins
2. *Inactivation of various substances :*
   - Toxins
   - Steroids
   - Other hormones
3. *Synthesis of plasma proteins :*
   - Acute phase proteins
   - Albumin
   - Clotting factors
   - Steroid binding and other hormone binding proteins
4. *Immunity*
   - Kupffer cells.

(Ref. Ganong 22th Edition, Page 500)

Storage function of liver

Liver is the storage house of the body. It can storage carbohydrate, protein and fat as glycogen. It also storage certain vitamins, iron. Liver is the one of the major blood reserviors.

1. *Storage of glycogen :* When blood glucose level rises liver converts all the glucose into glycogen by the glycongenesis and stored them. It also converts the fat and protein into glucose by the process of neoglucogenesis and then stored them as glycogne.
2. *Storage of vitamins :* Liver has a particular propensity for storing vitamins and act as a excellent source of certain vitamins during their deficiency. It can stored vitamin-A to a greatest extent but large quantity of vit-D and vit-B_{12} are normally stored.
3. *Storage of irons :* The greater portion of iron in the body is stored in the liver in the form of ferritin. The hepatic cell contain a protein called apoferritin which combines with iron and convert them into ferritin and stored until needed.
4. *Storage of blood :* An icrease in pressure in the veins draining the liver dams blood in the liver sinosoids and there by causes the entire liver to swell. In this way liver stored about 200 ml to 400 ml of blood.

Liver function tests

A. Biochemical tests :

1. *Synthetic function tests :*
   - i. Total protein concentration
   - ii. Serum albumin & globulin level
   - iii. Albumin-globulin ratio (Normal- 1.7 : 1)
   - iv. Prothrombin time (Normal : 12-16 second)
2. *Excretory function test :*
   - i. Serum bilirubin level
   - ii. Urine bilirubin
   - iii. Urine urobilinogen
   - iv. Stool stercobilinogen
3. *Metabolic function test :*
   - i. Glucose tolerance test
   - ii. Galactose tolerance test
   - iii. Serum cholesterol level
4. *Serum enzymes :*
   - i. Alanine aminotransferase (ALT) / Serum glutamate pyruvate test (SGPT)
   - ii. Aspertate aminotransferase (AST) / Serum glutamate oxaloacetate test (SGOT)
   - iii. Alkaline phosphatase
   - iv. γ-glutamyl transferase
5. Bromsulphthaline clearance test - very rarejy done.
6. Other determination : Ferritin
   - i. Iron binding.c~pacity saturation
   - ii. Alpha 1 -antitrypsin

     α-fetoprotein : normaly produced by fetal liver.
   - iii. Ceruloplasmin
   - iv. Copper

B. Serological test :
   - i. Viral antigens and antibodies
   - ii. Autoantibodies.

Use of liver function test

1. Differential diagnosis of jaundice.
2. Diagnosis of liver damage.
3. To asses the extent of liver damage.
4. To follow the progress of liver.

Galactose tolerance test :

Procedure : Normally galactose is absorbed from the intestine and converted into glucose in the liver. 40 gm of galactose in 400 ml of water is given to a fasting subject and blood galactose level is determined at 40, 60, 90, 120 minutes interval. In healthy individual, there is hardly any rise of blood glucose. The normal galactose index: 68-160. Galactose index above 160 indicates hepatic damage.

Oral glucose tolerance test- OGTT

a. *Procedure* : The individual should be on a normal diet at least for 3 days and is to fast overnight (10-16 hours).

Test :

1. Fasting venous blood for plasma and urine samples are collected.
2. 75 gm glucose in 250-300 ml water is given by mouth.
3. Venous blood and urine samples are collected either at the end of 2 hours or at half hourly intervals for 2 to 2 hours 30 minutes
4. Plasma glucose on each sample is estimated. Sugar on each sample is examined.

b. *Result* :

	Normal	*Diabetes mellitus*
i. Fasting	Less than 5.5	7.8 or more
ii. 2 hours after 75 gm glucose	Less than 7.8	1.11 or more

Normal renal threshold of glucose is usually 180 mgldl. Diabetes of long standing often have elevated renal threshold.

Thus, a patient can be diagnosed as diabetic on the basis of OGTT & fasting blood glucose concentration.

Bile

Characteristics :

1. Quantity : 600 - 1000 ml/day (Guyton 10th, P-749)
   500 ml/day (Ganong 20th, P-485)
2. Colour : Yellowish green
3. Consistancy : Viscid, mucoid liquid
4. Reaction : Alkaline
5. PH : a. *Liver bile* : 7.6 - 8.6
   b. *Gall bladder bile* : 6.8 - 7.8
6. Taste : Bitter.

(Ref. Ganong 22th, P-501; Guyton 11th, P-803 & others)

Formation of bile

Bile is made up of the bile salts, bile pigments, and other substances dissolved in an alkaline electrolyte solution that resembles pancreatic juice.

About 500 ml is secreted per day. Some of the components of the bile are reabsorbed in the intestine and then excreted again by the liver (enterohepatic circulation).

Bile pigments : The glucuronides of the *bile pigments*, bilirubin and biliverdin, are responsible for the golden-yellow color of bile. These are the breakdown products of hemoglobin.

Bile salts : The bile salts are sodium and potassium salts of bile acids, and all those secreted into the bile are conjugated to glycine or taurine, a derivative of cysteine.

Bile acids : The bile acids are synthesized from cholesterol. The four found in humans are listed in Figure 26-22. In common with vitamin D, cholesterol, a variery of steroid hormones, and the digitalis glycosides, the bile acids contain the cyclopentanoperhydroPhenanthrene nucleus. The two principal (primary) bile acids formed in the liver are *cholic acid* and *chenodeoxycholic acid*. In the colon, bacteria convert cholic acid to deoxycholic acid and chenodeoxycholic acid to lithocholic acid. Since they are formed by bacterial action deoxycholic acid and chenodeoxycholic acid are called secondary biles acids.

(Ref. Ganong 22th Edition; page 504, 505)

Composition of liver and gall bladder bile

Costituents	*Liver bile*	*Gall bladder bile*
Water	97.5 g/dl	92 g/dl
Bile salts	1.1 g/dl	6 g/dl
Bilirubin	0.04 g/dl	0.3 g/dl
Cholesterol	0.1 g/dl	0.3 to 0.9 g/dl
Fatty acids	0.12 g/dl	0.3 to 1.2 g/dl
Lecithin	0.04 g/dl	0.3 g/dl
Na^+	145 mEq/L	130 mEq/L
K^+	5 mEq/L	12 mEq/L
Ca^{++}	5 mEq/L	23 mEq/L
Cl^-	100 mEq/L	25 mEq/L
HCO_3^-	28 mEq/L	10 mEq/L

(Ref. Guyton & Hall-11th Edition, Page 803)

Pathway of bile secretion

Hepatic cell → Bile canaliculi → Intralobular bile ductule → Inter lobular bile ductule → Right and left hepatic duct → Common hepatic duct → Cystic duct → Gall bladder → Cystic duct → Bile duct → Hepato pancreatic ampulla → Duodenum.

Function of bile

1. *Digestive function :*
   Bile helps in the digestion of fat and to a lesser extent of proteins and carbohydrates with the help of bile salt which acts in the following way -
   i. *By reducing surface tension :* By this fat is converted into emultion by broken down into samller molecules and increases the surfac area. So the process of digestion is quickened.
   ii. *By activating the action of lipase :* It is due to cholic acid.
   iii. *By solvent action :* It acts as a good solvent, so enzyme acts on aqueous solution.
2. *Absorptive function :* With the help of bile salts, bile help in the absorption of fat and other substances like fat soluble vitamins, iron, calcium etc.

3. *Cholagogue action :* Increases the secretion of bile from liver.
4. *Laxative function :* Bile salts increases peristalsis and thereby help in daefecation.
5. *Excretory function :* Certain substances are excreted through bile :
   i. Heavy metals : Cu, Zn, Hg, etc.
   ii. Certain drugs
   iii. Bile pigments- bilirubin etc.
   iv. Cholesterol
   v. Toxin, Bacteria.
6. *Mucin of bile acts as buffer and lubricant.*

(Ref. Guyton & Hall-11th Edition, page 802 & others)

Bile salts

Name of bile salts :

1. Na tauro-cholate, K tauro-cholate.
2. Na glycholate, K glycholate.

Synthesis of bile salt :

1. Taurine + Cholic acid → Taurocholic acid
   Taurocholic acid + Na → Na taurocholate
   Taurine is the derivatives of cystin.
2. Glycin + Enolic acid → Glycholic acid
   Glycholic acid + Na → Na Glycholate.

Function of the bile salt :

1. *Emulsifying or detergent function :* Bile salts decreases the surface tention of the particle and allows the intentional agitation to break the fat glubules into minute sizes.
2. *Absorptive function :* Bile salts help in the absorption of fatty acids, monoglycerides, cholesterol and other lipids from the intestinal tract by forming minute complexs with these lipid called micelles. It also help in the absorption of fat soluble vitamins, iron, calcium etc.

(Ref. Guyton & Hall-11th Edition, page 804)

Entero-hepatic circulation of bile salts

After secretion into the intestine from gallbladder, 94% of bile salt are reabsorbed into the blood fromthe small intestine, about one half of this by *diffusion* through the mucosa in the early portions of the small intestine and the remainder by an active transport process through the intestinal mucosa in the distal ileum. They then enter the portal blood and pass back to the liver.

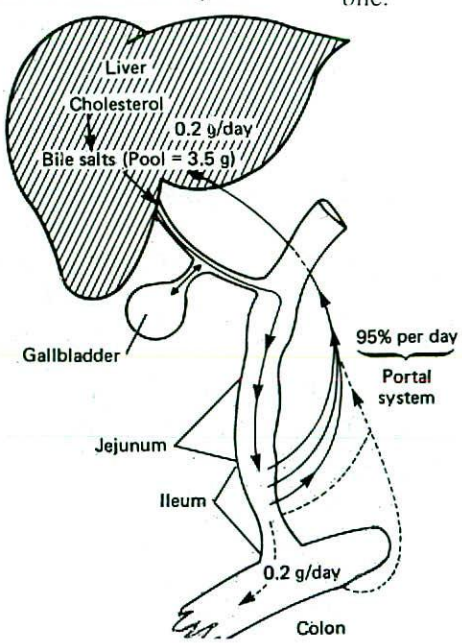


Fig. 10-5. *Entero Hepatic Circulation of Bile Salt.*

On reaching the liver, the bile salts are reabsorbed from the venous sinusoids into the hepatic cells and thus resecreted into the bile. In this way about 94% of all the bile salts are recirculated into the bile. So that on the average, these salts make the entire circuit some, 18 times before being carried out in the feces. These recirculation of bile salts is called entero-hepatic circulation of bile salts.

(Ref. Guyton & Hall-11th Edition, page 804)

Bile Acids

1. Cholic acid.
2. Deoxycholic acid.
3. Cheno-deoxycholic acid.
4. Lethocholic acid.
5. Enolic acid.

Bile pigment

1. Bilirubin
2. Biliverdin.

Gall Bladder

Functions of gall bladder :

1. Gall bladder absorbs H_2O and concentrates bile about 10-20 times.
2. It acts as a store house of bile.
3. It helps in the intermittent flow of bile.
4. It absorbs inorganic salts from bile to some extent and reduced the alkalinity of liver bile.
5. It excretes cholesterol to some extent.
6. It secretes mucous which is the main source of mucin in bile.

Mechanism of emptying of Gall bladder

Two basic conditions are required for the emptying of gall bladder-

i. Contraction of gall bladder.
ii. Simultaneous relaxation of sphincter of oddi.

Both this effect takes place in the following ways :

1. *Presence of fat and partially digested protein* in the upper part of small intestine causes release of hormone cholecystokinin from the intestinal mucosa passes to gall bladder via blood causes specific contraction of gall bladder that provides the pressure required to move bile towards duodenum.
2. *Vagal stimulation :* Stimulation of vagus nerve during cephalic phase of gastric secretion or during various intestino-

intestinal reflexes causes additional weak contraction of gall bladder and emptying of it occurs.

3. *Cholecystokinin :* Directly acts on the sphincter of oddi causing relaxation of it. In addition during contraction of gall bladder a neurogenic signal also inhibit the sphincter of oddi that causes flow of bile from the common bile duct into duodenum.
4. *The presence of food in the duodneum* - Causes the degree of peristalsis in the duodenal wall to increase. Each time a peristaltic wave travels toward the sphincter of oddi, causes relaxation of it, by the phenomenon receptive relaxtion. Causes flow of bile from the bile duct in to the duodenum.

(Ref. Guyton & Hall-11th Edition, Page 803)

Cholagogue : Any agent which increases the flow of bile from gall bladder into the intestine is known as cholagogue.

Choleratic : Any agent which increases the output of bile from liver, without changing its necessary constituentse. g - Bile salts, fat etc.

Hydrocholcratic : Any agent which increases the volume of bile without corresponding increases in bile solids.

Mechanism of gall stone formation

Under abnormal conditions the cholesterol may precipitate, resulting in the formation of gall stones.

The different conditions that can cause cholesterol precipitation are :

1. Too much absorption of water from the bile.
2. Too much absorption of bile salts and lecithin from the bile.
3. Too much secretion of cholesterol in the bile.
4. Inflammation of epithelium of the gall bladder.

The latter two of these require the following special explanation : The amount of ***cholesterol*** in the bile is determined partly by the quantity of fat that the person eat, for the hepatic cells synthesize cholesterol as one of the products of fat metabolism in the body. For this reason, persons on a high fat diet over a period of many years are prone to the development of gall stones.

Inflammation of the gall bladder epithelium often results from low grade chronic infection; this changes the absorptive characteristics of the gall bladder mucosa, sometimes allowing excessive absorption of bile salts, or other substances that are necessary to keep the cholesterol in solution. As a result, cholesterol begins to precipitate, usually forming many small crystals of cholesterol on the surface of the inflammed mucosa. These, in turn, act as nidi for further precipitation of cholesterol, and the crystals grow larger and larger. Occasionally tremendous numbers of sandlike stones develop, but much more frequently these coalesce to form a few large galls tones, or even a single stone that fills the entire gall bladder. Also, calcium ions, which are usually concentrated five or more fold in the gall bladder, often precipitate in the gall stones, making them x-ray opaque so that they can be seen in radiographs of the abdomen.

(Ref. Guyton & Hall-11th Edition, page 804)

Digestion & Absorption

Digestion

Basic mechanism of digestion : The basic mechanism of disgestion is hydrolysis. Almost all the carohydrates of the diet are large poly-saccharides or disaccharides, which are the combination of many mono saccharides bind to each other by the process of condensation. This mean that a H^+ is removed from one of the mono saccharide while $OH^-$is removed from the next one, this two mono saccharides then combines with each other at the sites of removal and the H^+ and OH combines to from water. When carbohydrates are digested back into mono saccharides, specific enzymes return the H^+ & OH^- to the polysaccha- rides and thereby seperate the monosaccharides from each other. This process is known as hydrolysis.

$$R_1 + R_2 + H_2O \xrightarrow{\text{Digestive Enzymes}} R_1OH + R_2H$$

(Ref. Guyton & Hall-11th Edition, page 808)

Absorption

Definition : Absorption is the process by which the end products of digestion pass through the intestinal epithelium and enter the blood stream.

Anatomical basis of absorption : The stomach is a poor absorptive area of the gastrointestinal tract because it lacks the typical villus type of absorptive membrane and because the junctions between the epithelial cells are tight junctions, only a few highly lipid soluble substances, such as *alcohol*,and some drugs like *aspirin*, can be absorbed in small quantities.

(Ref. Guyton & Hall-11th Edition, page 812)

Absorptive surface of the small intestinal mucosa- *The villi* :

1. *Valvulae conniventes or folds of Kercking* : These folds extend circularly most of the way arround the intestine specially in duodenum and jejunum which increase the surface area of absorptive mucosa about 3 fold.
2. *Villi (millions in number)* : These project about 1 mm from the surface of the mucosa and enhances the absorptive area another 10 fold.
3. *Brush border consisting of microvilli (1 micro meter in length, 0.1 micro meter in diameter)* : These increases the absorptive area another 20 fold.

Thus the combination of folds of Kercking, the villi and

the micro vill increases the absorptive area of the mucosa about 1000 fold, making tremendous total area of about 250 square meters for the entire intestine.

(Ref Guyton & Hall-11th Edition, page 812, 813)

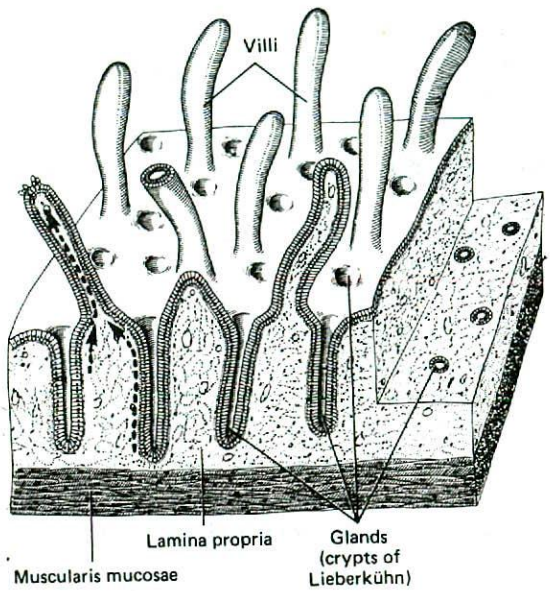


Fig. 10-7. *Structure of the small intestine. The epithelium linning the glands continues over the villi. Mucosal cells are formed in the glands and migrate up to the tips of the villi, where they are shed into the intestinal lumen.*

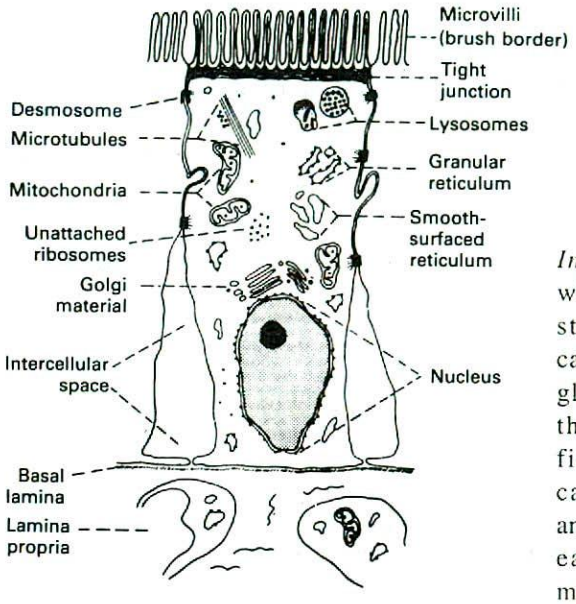


Fig. 10-8. *Diagram of enterocytes; the microvilli, the tight connections of cells at the mucosal edge (desmosomes), and the space between the cells at base (intercellular space).*

Basic mechenisms of absorption : Most substances must pass from the intestinal lumen into the mucosal cells (enterocytes) and then out of the enterocytes to the interstitial fluid, and the processes responsible for movement across the luminal cell membrane are often quite different from those responsible for movement across the basal and lateral cell membranes to the interstitial fluid.

(Ref. Ganong 22th edition, Page-467)

Carbohydrate

Carbogydrate digestion

Carbohydrate foods of the diet : Only three major sources of carbohydrates exist in the normal human diet.

They are :

i. *Sucrose*, which is the *disaccharide* known popularly as cane sugar.

ii. *Lactose*, which is a *disaccharide* in milk.

iii. *Starches*, which are large *polysaccharides* present in almost all nonanimal foods and particularly in the grains.

iv. *Other carbohydrates* ingested to a slight extent are amylose, glycogen, alcohol, lactic acid, pyruvic acid, pectins, dextrins, and minor quantities of carbohydrate derivatives in meats.

v. *Cellulose* : The diet also contains a large amount of cellulose, which is a carbohydrate.

However, no enzymes capable of hydrolyzing cellulose are secreted in the human digestive tract. Consequently, cellulose cannot be considered a food for the human being.

In the ordinary diet, which contains far more starches than all other carbohydrates combined, glucose represents more than 80 percent of the final products of carbohydrate digestion, and galactose and fructose each seldom represent more than 10 percent of the products of carbohydrate digestion.

(Ref. Guyton & Hall 11-th Edition, Page 809)

The digestion of carbohydrate in different part of GI tract occurs as follows :

1. *In the mouth* : When food is chewed, it is mixed with saliva, which contains the enzyme ptyalin (an α-amylase) secreted mainly by the parotid glands. This enzyme hydrolyzes starch into the disaccharide maltose and other small polymers of glucose that contain three to nine glucose molecules. But the food remains in the mouth only a short time, and probably not more than 5% of all the startches that are eaten will have hydrolyzed by the time the food is swallowed.

$$\text{Starches} \xrightarrow{ptyalin} \text{Maltose and 3 to 9 glucose polymers}$$

2. *In the stomach* : However, starch digestion continues in the body and fundus of the stomach for as long as 1 hour before the food becomes mixed with the stomach secretions. Then the acidity of the salivary amylase is blocked by the acid of the gastric secretions because it is essentially nonactive as an enzyme once the pH of the medium falls below about 4.0. Nevertheless, on the average, before the food and its accomaining saliva do become completely mixed with the gastric secretions, as much as 30 to 40 per cent of the starches will have been hydrolyzed mainly to maltose.

3. *In the small intestine (Luminal digestion)* : Within 15 to 30

minutes after the empties from the stomach into the duodenum and mixes with pancreatic juice, vartually all the starches will have been digested. In general starches are almost totally converted into *maltose and other very small glucose polymers* before they have passed beyond the duodenum and upper jejunum.

Starch and dextrins —*Pancreatic α-amylase*→ Maltose and other very small glucose polymers.

4. *Membrane digestion (Digestion by enterocytes enzymes)* : The carbohydrate splitting enzymes of small intestine (maltase, lactase, alpha-dextrinase, sucrase, trehalase) are secreted from the enterocytes lining the villi of the small intestine and digest all the disaccharide in the following way

   a. Maltose —*Maltase 25 %, α-Dextrinase 50% , Sucrase 25%*→ Glucose + Glucose

   b. α-Dextrins —*α-Dextrinase 95% , Maltase 25%*→ Glucose + Glucose

   c. Maltotriose —*α-Dextrinase 95% , Maltase 25% , Sucrase 25%*→ Glucose + Glucose

   d. Lactose —*Lactase 100%*→ Glucose + Galactose

   e. Sucrose —*Sucrase 100%*→ Glucose + Fructose

   f. Trehalose —*Trehalase 100%*→ Glucose.

(Ref. Guyton & Hall-11th Edition, Page 809; Ganong 22th Edition; page 467)

N.B. Deficiency of one or more of the brush border *oligosaccharidases* may cause *diarrhea, bloating, and flatulence* after ingestion of sugar. The ***diarrhea*** is due to the increased number of osmotically active oligosaccharide molecules that remain in the intestinal lumen, causing the volume of the intestinal contents to increase. In the colon, bacteria break down some of the oligosaccharides, further increasing the number of osmotically active particles. The ***bloating*** and ***flatulance*** are due to the production of gas (CO_2 and H^+) from disaccharide reduces in the lower small intestine and colon.

Lactase is of interest because, in most mammals and in many races of humans, intestinal lactase activity is high at birth, then declines to low levels during childhood and adulthood. The low lactase levels are associated with intolerance to milk (***lactose intolerance***). Most Europeans and their American descendants retain their intestinal lactase activity in adulthood; the incidence of lactase deficiency in northern and western Europeans is only about 15%. However, The incidence in the blacks, American Indians, Orientals, and Mediterranean populations is 70-100%. Milk intolarence can be ameliorated by administration of commercial lactase preperations, but this is expensive. Yogurt is better tolerated than milk in intolerant individuals because it contains its own bacterial lactase.

(Ganong 21th edition, Page-471-474)

Absorption of carbohydrate

The end product of carbohydrate digestion are monosaccharide, disacchride. About 80% of monosaccharides are absorbed in the form of glucose and other in the form of galactose, fructose etc.

Absorption of glucose & galactose : Glucose and galactose are absorbed by the active process with the help of carrier by a process called sodium co-transport theory for glucose transport.

It is known that the carrier protein for transport of glucose present in the brush border of the epithelial cell. It is believed that the carrier protein has receptor sites for both a glucose molecule and a sodium ion. Glucose is transported whenever Na^+ is transported. The sodium binds with the receptor and transported with the help of energy from intestine to the interior of the intestinal epithelial cell and at the same time it pulls the glusose along with it. Then from the cell, glucose is transported into blood stream by the facilated diffusion.

Absorption of fructose : It is transported by facilated diffusion all the way through the intestinal epithelium but not coupled with sodium transport. On entering the cell, much of the fructose becomes phosphorylated, then converted to glucose

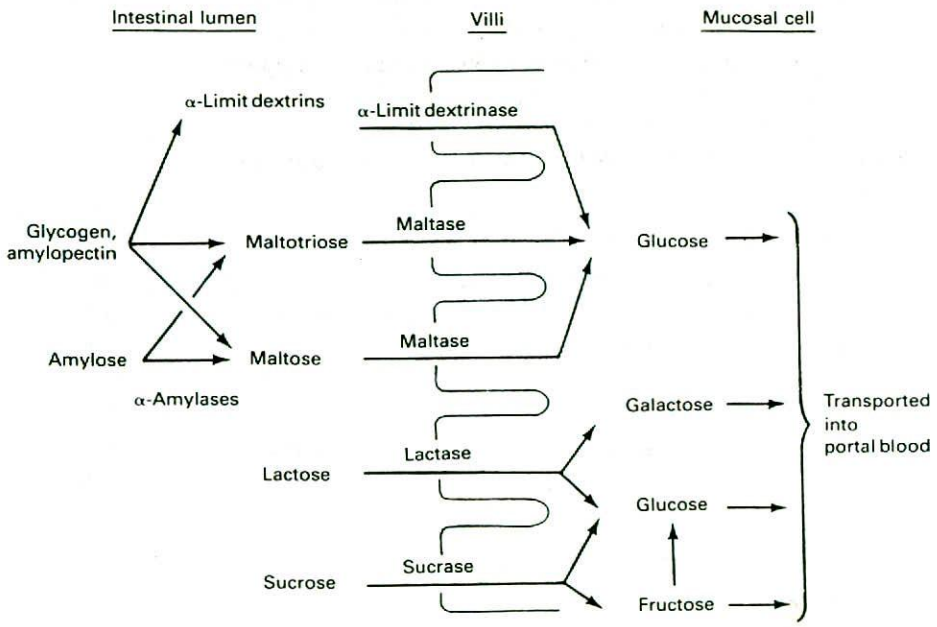


Table 10-9. *Outline of carohydrate digestion and adsorption.*

and finally transported in the from of glucose the rest of the way into the paracellular space.

(Ref. Guyton & Hall-11th Edition, Page 815, 816)

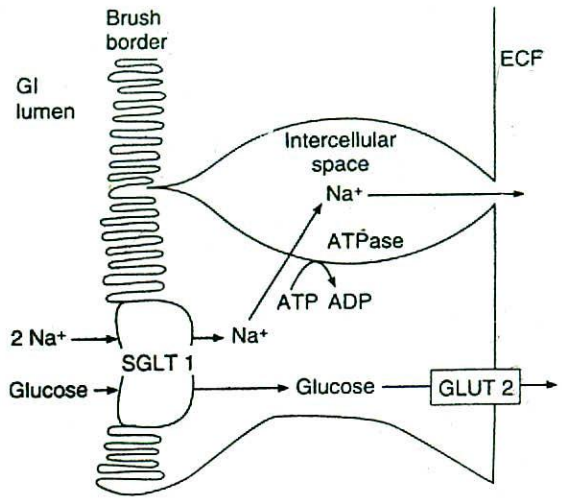


Figure 10-10. *Mechanism for glucose transport across intestinal epithelium. Glucose transport into the intestinal cell is coupled to Na^+ transport, utilizing the cotransporter SGLT 1. Na^+ is then actively transported out of the cell, and glucose enters the interstitium by facilitated diffusion via GLUT 2. From there, it diffuses into the blood.*

Protein

Digestion of protein

Proteins of the diet : The dietary proteins are formed of long chains of amino acids bound together by *peptide linkages*. The characteristics of each type of protein are determined by the types of amino acids in the protein molecule and by the arrangement of these amino acids.

The digestion of protein in different parts of GI tract occurs as follows :

1. *In the mouth :* No digestion of protein in the mouth.
2. *In the stomach :* In presence of pepsin and gastric HCl protein is converted into proteoses, peptones and a few polypeptides. Providing only 10-20 % of total protein digestion. A *gelatinase* that liquifies gelatin is also found in the stomach. *Chymosin*, a milk-clotting gastric enzyme also known as *renin*, is found in the stomachs of young animals but is probably absent in humans *(Ref. Ganong 22th, p-457).*

Protein —(*Pepsin*, *HCl*)→ Proteoses / Peptone / Polypeptides

3. *In the duodenum (Digestion of proteins by pancreatic secretions) :* Here trypsin and chymotrypsin of pancreatic juice act on broken and unbroken peptone and converts it into poly peptide.

Proteoses / Peptones —(*Trypsin, Chymotrypsi, Carboxy polypeptidase, Proelastase*)→ Poly peptides / Amino acids / Polypeptides

Carboxypolypeptidase then cleaves individual amino acids from the carboxyl ends of the polypeptides. *Proelastase* gives rise to elastase that in turn digests the elastin fibers that hold meats together.

Only a small percentage of the proteins are digested all the way to their constituent amino acids by the pancreatic juices. Most remains as dipeptides, tripeptides, and some even larger.

4. *Digestion of peptides by peptidases in the enterocytes that line the small intestinal villi mainly in the deudenum and jejunum :* The last digestion of the proteins in the intestinal lumen is achieved by the enterocytes that line the villi of the small intestine, mainly in the duodenum and jejunum. These cells have a brush border that consists literally of hundreds of microvilli projecting from the surface of each cell. In the cell membrane of each of these microvilli are multiple *peptidases* that protrude through the membranes to the exterior, where they come in contact with the intestinal fluids. Two types of peptidase enzymes are especially important, *aminopoly-peptidase* and several *dipeptidases*. They succeed in splitting the remaining larger polypeptides into tripeptides and dipeptides and a few all the way to amino acids. Both the amino acids and the dipeptides and tripeptides are easily transported through the microvillar membrane to the interior of the enterocyte.

Polypeptides / Amino acids —(*Peptidase*)→ Amino acids

Finally, inside the cytosol of the enterocyte are multiple other peptidases that are specific for the remaining types of linkages between the amino acids. Within minutes, virtually all the last dipeptides and tripeptides are digested to the final stage of single amino acids; they then pass on through the opposite side of the enterocyte into the blood. More than 99 percent of the final protein digestive products that are absorbed are individual amino acids, with only rare absorption of peptides, and very, very rare absorption of whole protein molecules. Even these very few molecules of protein can sometimes cause serious allergic or immunological disturbances.

(Ref. Guyton & Hall-11th Edition, Page 810)

Nucleic acids : Nucleic acids are split into nucleotides in the intestine by the *pancreatic nueleases*, and the nueleotides are split into the nucleosides and phosphoric acid by

enzymes that appear to be located on the luminal surfaces of the mucosal cells. The nucleosides are then split into their constituent sugars and purine and pyrimidine bases. The bases are absorbed by active transport.

(Ganong 22th edition, Page-473)

Absorption of protein

At least seven different transport systems transport amino acids into enterocytes. Five of these require Na^+ and cotransport amino acids and Na^+ in a fashion similar to the cotransport of Na^+ and glucose (Figure 13-9). Two of these four also require Cl^-. In two systems transport is independent of Na^+.

Di- and tripeptides are transported into enterocytes by a system that requires H^+ instead of Na^+. There is very little absorption of larger peptides. In the enterocytes, amino acids released from the peptides by intracellular hydrolysis plus the amino acids absorbed from the intestinal lumen and brush border are transported out of the enterocytes along their basolateral borders by at least five transport systems. From there, they enter the hepatic portal blood. Two of these systems are dependent on Na^+, and three are not. Significant amounts of small peptides also enter the portal blood.

(Ganong 22th edition, Page-472)

N.B. Absorption of amino acids is rapid in the duodenum and jejunum but slow in the ileum. Approxiniately 50% of the digested protein comes from ingested food, 25% from proteins in digestive juices, and 25% from desquamated mucosal cells. Only 2-5% of the protein in the small intestine escapes digestion and absorption. Some of the *ingested protein enters the colon* and is eventually digested by bacterial action. The protein in the stools is not of dietary origin but comes from bacteria and cellular debris. There is evidence that the peptidase activities of the brush border and the mucosal cell cytoplasm are increased by resection of part of the ileum and that they are independently altered in starvation. Thus. these enzymes appear to be subject to homeostatic regulation. In humans, a congenital defect in the mechanism that transports neutral amino acids in the intestine and renal tubules causes ***Hartnup disease***. A congenital defect in the transport of basic amino acids causes ***cystinuria***.

In infants, moderate amounts of undigested protems are also absorbed. The protein antibodies in maternal colostrum are largely secretory immunoglobulins (IgAs), the production of which is increased in the breast in late pregnancy. They cross the mammary epithelium by transcytosis and enter the circulation of the infant from the intestine, providing passive immunity against infections. Absorption is by endocytosis and subsequent exocytosis.

Protein absorption declines with age, but adults still absorb small quantities. Foreign proteins that enter the circulation provoke the formation of antibodies, and the antigen-antibody reaction occurring upon subsequent entry of more of the same protein may cause allergic symptoms. Thus, absorption of proteins from the intestine may explain the occurrence of allergic symptoms after eating certain foods. The incidence of food allergy in children is said to be as high as 8%. Certain foods are more allergenic than others. Crustaceans, mollusks, and fish are common offenders, and allergic responses to legumes, cows milk, and egg white are also relatively frequent.

Absorption of protein antigens, particularly bacterial and viral proteins, takes place in large *microfold cells* or ***M cells***, specialized intestinal epithelial cells that overlie aggregates of lymphoid tissue (Peyer's patches). These cells pass the antigens to the lymphoid cells, and lymphoblasts are activated. The activated lymphoblasts enter the circulation, but they later return to the intestinal mucosa and other epithelia, where they secrete IgA in response to subsequent exposures to the same antigen. This ***secretory immunity*** is an important defense mechanism.

(Ganong 22th edition, Page-472)

N.B. The blood of fasting animals contain 3-6 mgm of amino acid/100ml. After meal the amount rises to 8-10 m gm/100 ml of blood.

Fat (Lipids)

Digestion of fat

Fats of the diet : By far the most abundant fats of the diet are the *neutral fats*, also known as *triglycerides*, each molecule of which is composed of a glycerol nucleus and three fatty acids. Neutral fat is a major constituent in food of animal origin and much less so in food of plant origin.

In the usual diet are also small quantities of *phospholipids, cholesterol, and cholesterol esters*. The phospholipids and cholesterol esters contain fatty acid and therefore can be considered fats themselves. Cholesterol, on the other hand, is a sterol compound that contains no fatty acid, but it does exhibit some of the physical and chemical characteristics of fat; it is derived from fats, and it is metabolized similarly to fats. Therefore, cholesterol is considered, from a dietary point of view, a fat.

The digestion of fat in different parts of the GI tract occurs as follows :

1. *In the mouth* : No digestion of fat occurs in the mouth cavity.
2. *In the stomach* : Fat digestion may occur in the stomach because the fat splitting enzyme (gastric lipase) is present in the gastric juice but this enzyme is inactive in acid media.

   A small amount of triglycerides is digested in the stomach by *lingual lipase* that is secreted by lingual glands in the mouth and swallowed with the saliva. The amount of digestion is less than 10 percent and generally unimportant. Instead, essentially all fat digestion occurs in the small intestine.

3. *Digestion of fat in the intestine :* The main digestion of fat occurs in the duodenum and small intestine by *pancreatic lipase* with the help of bile salts. Bile salts at first emulsified the fat globules and broken them into simple form and increases the surface area of fat globules. Then the enzyme lipase act on the surface of fat globules and splits into free fatty acids and monoglycerides.

Emulcification of fat by bile acids and lecithin : Emulsifi cation is the process by which fat globules are broken down into simple form by the bile salts.

Bile salts have two parts-carboxyl or polar part which is highly soluble in water and a sterol part which is highly soluble in fat. Therefore, bile salts aggregate at surfaces of the fat globules in the intestinal contents with the carboxyl portion of bile salt, while the sterol portion is dissolves in the fat itself. These effect greatly decreases the interfacial tension of the fat. When the interfacial tension of a globule of non miscible fluid is low, this fluid on aggitation, can be broken up into may minute particles. As a result each time the diameter of the fat globules are decreased and the total surface area of the fat increases two times. This process is called emulsification. The lipase are water soluble compound and can attack the fat globules only on their surfaces.

$$\text{Fat} \xrightarrow{\textit{Bile + aggitation}} \text{Emulsified fat}$$

$$\xrightarrow{\textit{Pancreatic lipase}} \text{Fatty acid \& 2-monoglycerides.}$$

Digestion of triglycerides by pancreatic lipase : By far the most important enzyme for the digestion of triglycerides is pancreatic lipase in the pancreatic juice. This is present in enormous quantities in pancreatic juice, enough to digest all triglycerides that it can reach within a few minutes. In addition, the enterocytes of the small intestine contain a minute quantity of lipase known as enteric lipase, but this is usually unimportant.

End products of fat digestion : Most of the triglycerides of the diet are split by pancreatic lipase into free fatty acids and 2-monoglycerides, Minute portions remain in the diglyceride state.

(Ref. Guyton & Hall-11th Edition, Page811, 812)

Role of bile salts in accelerating fat digestion, formation of Micelles : Micelles are spherical globules about 3-4 nano meter in diameter and composed of 20 to 40 molecules of bile salts. The sterol nuclei of 20 to 40 bile salt molecules of the micelles aggregate together to form a small fat globules in the middle of micelles. This aggregation causes pollar group of the micelle to project outwards to cover the micelle. Since this pollar group are negatively charges, they allow the entire micelle globule to become dissolved in the water of the digestive fluid.

During triglycerides digestion, as rapidly as the monoglycerides and fatty acids are formed they become dissolved in the fatty portion of the micelles and transported to the surface of the epithelial cell.

(Ref. Guyton & Hall-11th Edition, Page 812)

Digestion of cholesterol esters and phospholipids : Most of the cholesterol in the diet is in the form of cholesterol esters, which are combinations of free cholesterol and one molecule of fatty acid. Phospholipids also contain fatty acid chains within their molecules. Both the cholesterol esters and the phospholipids are hydrolyzed by two other lipases in the pancreatic secretion that free the fatty acids-the enzyme cholesterol ester hydrolase to hydrolyze the cholesterol ester and phospholi -pase A_2 to hydrolyze the phospholipid.

The bile salt micelles play the same role in *"ferrying"* free cholesterol and the remaining portions of the digested phospho lipid molecules as they play in *"ferrying"* mono glycerides and free fatty acids. Indeed, this role of the micelles is essential to the absorption of cho -lesterol becasues essentially no cholesterol can be absobed without the function of the micelles. On the other hand, as much as 60 percent of the triglycerides can be digested and absorbed even in the absence of the bile salt micelles.

(Ref. Guyton & Hall-11th Edition, Page 812)

Absorption of fat

Fats are digested to form *monoglycerides* and *free fatty acids*, both of these digestive end products become dissolved in the central lipid portion of the *bile micelles*. Because of the molecular dimensions of these micelles, only 3 to 6 nanometers in diameter, and because of their highly charged exterior, they are soluble in the chyme. In this form, the monoglycerides and the fatty acids are carried to the surfaces of the microvilli of the intestinal cell brush border and then penetrate into the recesses among the moving, agitating microvilli. Here, both the monoglycerides and the fatty acids diffuse immediately from the micelle and then through the membrane of the microvillii to the interior of the cell; this is possible because these lipids are also soluble in the epithelial cell membrane. This leaves the bile micelles still in the chyme, where they function again and again to help absorb still more monoglycerides and fatty acids. Thus, the micelles perform a *'ferrying'* function that is highly important for fat absorption. In the presence of an abundance of bile micelles, about 97 per cent of the fat is absorbed; in the absence of the bile micelles, only 40 to 50 per cent is normally absorbed.

The ***fate of the fatty acids in enterocytes*** depends on their size. Fatty acids containing less than 10-12 carbon atoms pass from the mucosal cells directly into the portal blood, where they are transported as free (unesterified) fatty acids. The fatty acids containing more than 10-12 carbon atoms are reesterified to

triglycerides in the mucosal cells. In addition, some of the absorbed cholesterol is esterifled. The triglycerides and cholesteryl esters are then coated with a layer of protein, cholesterol, and phospholipid to form ***chylomicrons***. These leave the cell and enter the lymphatics.

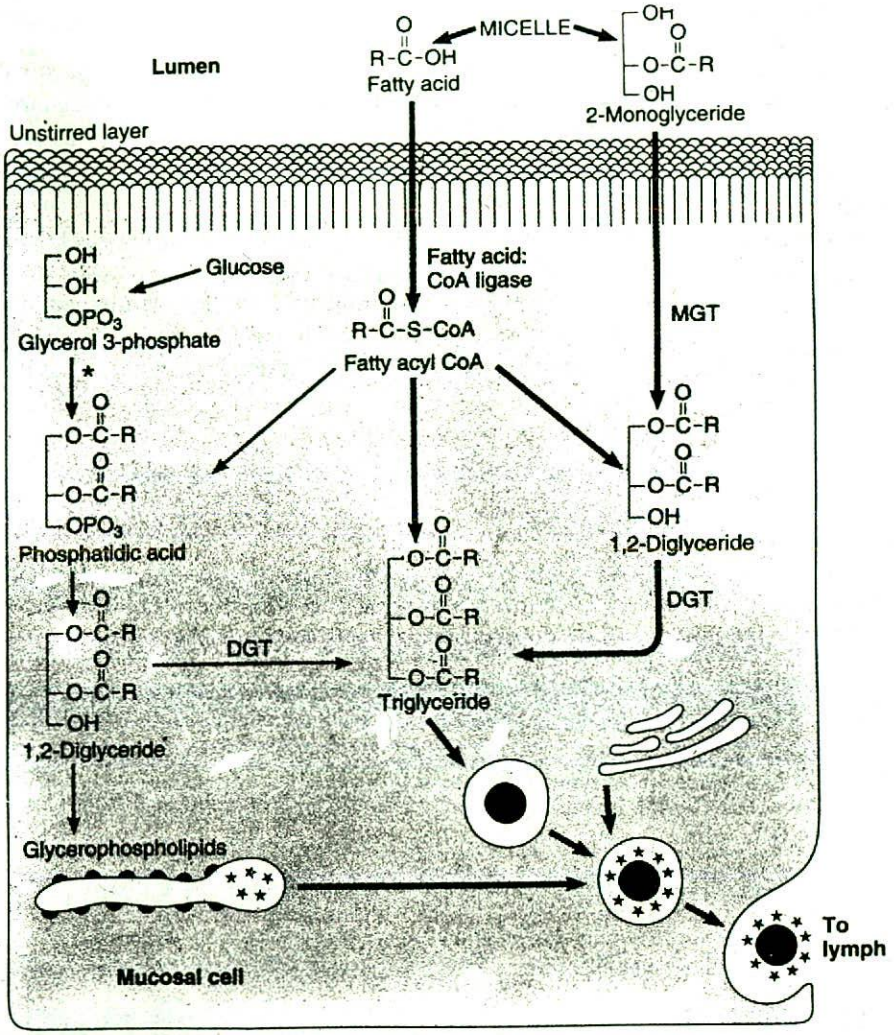


Figure 10-11. *Lipid absorption. Triglycerides are formed in the mucosal cells from monoglycerides and fatty acids. Some of the glycerides also come from glucose via phosphatidic acid. The triglycerides are then converted to chylomicrons and released by exocytosis. From the extracellular space, they enter the lymph. Heavy arrows indicated major pathways.*, reaction inhibited by monoglyceride; MGT, monoacylglycerol acyltransferase; DGT, diacylglycerol acyltransferase.*

In mucosal cells, most of the triglyceride is formed by the acylation of the absorbed 2-monoglycerides, primarily in the smooth endoplasmic reticulum. However, some of the triglyceride is formed from glycerophosphate, which in turn is a product of glucose catabolism. Glycerophosphate is also converted into glycerophospholipids that participate in chylomicron formation. The acylation of glycerophosphate and the formation of lipoproteins occur in the rough endoplasmic reticulum. Carbohydrate moieties are added to the proteins in the Golgi apparatus, and the finished *chylomicrons are extruded by exoeytosis* from the basal or lateral aspects of the cell.

Absorption of long-chain fatty acids is greatest in the upper parts of the small intestine, but appreciable amounts are also absorbed in the ileum.

The processes involved in fat absorption are not fully mature at birth, and infants fail to absorb l0-15% of ingested fat. Thus, they are more susceptible to the ill effects of disease processes that reduce fat absorption.

(Ganong 22th edition, Page-474, 475)

Short-chain fatty acids in the colon : Increasing attention is being focused on short-chain fatty acids (SCFAs) that are produced in the colon and absorbed from it. SCFAs are two-to five-carbon weak acids that have an average normal concentration of about 80 mmol/L in the lumen. About 60% of this total is acetate, 25% proprionate, and 15% butyrate. They are formed by the action of colonic bacteria on complex carbohydrates, resistant starches, and other components of the dietary fiber, ie, the material that escapes digestion in the upper gastrointestinal tract and enters the colon.

Absorbed SCFAs are metabolized and make a significant contribution to the total caloric intake, in addition, they exert a trophic effect on the colonic epithehal cells, combat inflammation, and are absorbed in part by exchange for H^+, helping to maintain acid-base equilibrium. There are a family of anion exchangers in the colonic epithelial cells. SCFAs also promote the absorption of Na^+, although the exact mechanism for coupled Na^+-SCFA absorption is unsettled.

(Ganong 22th edition, Page 475)

Absorption of cholesterol & other sterols : Cholesterol is readily absorbed from the small intestine if bile, fatty acids, and pancreatic juice are present. Closely related sterols of plant origin are poorly absorbed. Almost all the absorbed cholesterol is incorporated into chylomicrons that enter the circulation via the lymphatics, as noted above. Nonabsorbable plant sterols such as those found in *soybeans reduce the absorption of cholesterol*, probably by competing with cholesterol for esterification with fatty acids.

(Ganong 22th edition, Page 475)

Absorption of water & electrolytes

Water : The intestines are presented each day with about 2000 ml of ingested fluid plus 7000 ml of secretions from the mucosa of the gastrointestinal tract and associated glands.

Ninety eight percent of this fluid is reabsorbed, with a daily fluid loss of only 200 ml in the stools. Only small amounts of water move across the gastric mucosa, but water moves in both directions across the mucosa of the small and large intestines in response to osmotic gradients.

Water moves into or out of the intestine until the osmotic pressure of the intestinal contents equals that of the plasma. The osmolality of the duodenal contents may be hypertonic or hypotonic, depending on the meal ingested but by the time the meal enters the jejunum, its osmolality is close to that of plasma. This osmolality is maintained throughout the rest of the small intestine ; the osmotically active particles produced by digestion are removed by absorption, and water moves passively out of the gut alone the osmotic gradient thus generated.

In the colon ; Na^+ is pumped out and water moves passively with it, again along the osmotic gradient. Saline cathartics such as magnesium sulfate are poorly absorbed salts that retain their osmotic equivalent of water in the intestine, thus increasing intestinal volume and consequently exerting a laxative effect.

(Ganong 22th Edition; page 475)

Daily water turnover (ml) in the gastrointestinal tract

Ingested		***2000***
Endogenous secretions		***7000***
Salivary glands	1500	
Stomach	2500	
Bile	500	
Pancreas	1500	
Intestine	1000	
	7000	
Total Input		***9000***
Reabsorbed		***8800***
Jejunum	5500	
Ileum	2000	
Colon	1300	
	8800	
Balance in stool		***200***

Data from Moore EW ; Physiology of Intestinal Water and Electrolyte Absorption. American Gastroenteorological Society. 1976.

(Ganong 22th edition, Page-476)

Sodium : Some Na^+ diffuses into or out of the small intestine depending on the concentration gradient. Because the luminal membranes of all enterocytes in the small intestine and colon are permeable to Na^+, and their basolateral membranes contain Na^+-K^+ ATPase. Na^+ is also actively absorbed throughout the small and large intestines.

In the small intestine, active transport of Na^+ is important in bringing about absorption of glucose, some amino acids and other substances. Conversely, the presence of glucose in the intestinal lumen facilitates the reabsorpton of Na^+.

(Ganong 22th edition, Page-476)

Potassium : There is some seeretion of K^+ into the intestinal lumen, especially as a component of mucus, but for the most part, the movement of K^+ across the gastrointestinal mucosa is due to diffusion. On the other hand, there are K^+ channels in luminal as well as the basolateral membrane of the enterocytes of the colon, so K^+ is secreted into the colon. In addition, K^+ moves passively down its electrochemical gradient. The accumulation of K^+ in the colon is partially offset by H^+-K^+ ATPase in the luminal membrane of cells in the distal colon, with resulting active transport of K^+ into the cells. Nevertheless, loss of ileal or colonic fluids in chronic diarrhoea can lead to severe hypokalemia.

(Ganong 22th edition, Page-476)

Chloride : Cl^+ normally enters enterocytes from the interstitial fluid via Na^+-K^+-$2Cl^-$ co-transporters in their basolateral membranes and the Cl^- is then secreted into the intestinal lumen via channels that are regulated by various protein kinases. One of these is activated by protein kinase A and hence by cAMP.

(Ganong 22th edition, Page-476)

Chloride & Bicarbonate : In the ileum and the colon, it appears that Cl^- is actively reabsorbed in a one-for-one exchange for HCO_3^-. This tends to make the intestinal contents more alkaline. However, the physiologic significance of this exchange is uncertain.

Absorption of Vitamins & Minerals

Vitamins : Absorption of water-soluble vitamins is rapid, but absorption of the fat-soluble vitamins A, D, E and K is deficient if fat absorption is depressed because of lack of pancreatic enzymes or if bile is excluded from the intestine by obstruction of the bile duct. Most vitamins are absorbed in the upper small intestine, but vitamin B_{12} is absorbed in the ileum. This vitamin binds to intrinsic factor, a protein secreted by the stomach, and the complex is absorbed across the ileal mucosa.

Vitamin B_{12} absorption and folate absorption are Na^+ independent, but all seven of the remaining water-soluble vitamins- thiamine, riboflavin, niacin, pyridoxine, pantothenate, biotin and ascorbic acid are absorbed by carriers that are Na^+ cotransporters.

(Ganong 22th edition, Page-477)

Calcium : From 30 to 80% of ingested calcium is absorbed .

Active transport of Ca^{++} out of the intestinal lumen occurs primarily in the upper small intestine, and there is also some absorption by passive diffusion. Active transport is facilitated by 1, 25 dihydroxycholecalciferol, the metabolite of vitamin D that is produced in the kidneys. The metabolite induces the synthesis of two forms of a Ca^{+}-binding protein in the mucosal cells and several forms of Ca^{+}-H^{+} ATPase. However, the details of the way the metabolite stimulates absorption remain unsettled. The rate of production of 1, 25 dihydroxycholecalci-ferol is increased when the plasma calcium level is decreased and reduced when the plasma calcium level is elevated . Consequently, Ca^{++} absorption is adjusted to body needs ; absorption is increased in the presence of Ca^{++} deficiency and decreased in the presence of Ca^{++} excess. Ca^{++} absorption is also facilitated by protein. It is inhibited by phosphates and oxalates because these anions form isoluble salts with Ca^{++} in the intestine. Magnesium absorption is facilitated by protein.

(Ganong 22th edition, Page-477)

Action of Bacterial Flora on Food

1. ***Carbohydrate*** *:* The changes brought about on carbohydrate are known as fermentation. A group of bacteria (bacillus cellulose dissolvens-BCD) also break down the cellulose.

   Carbohydrate $\xrightarrow{Bacteria}$ i. Lower fatty acids (Lactic, acetic, propionic, butyric and benzoic).
   ii. Gases-CO_2, CH_4, and H_2.

   Cellulose $\xrightarrow{BCD}$ i. Acid- butyric acid.
   ii. Alcohol-ethyl alcohol.
   iii. Gases - CO_2, H_2 .

2. *Fat* : Bacteria hydrolyzes fat into glycerol and fatty acids.
   i. Fat $\xrightarrow{Bacteria}$ Glycerol & fatty acids.
   ii. Phospholipid $\xrightarrow{Bacteria}$ Choline $\rightarrow$ toxic neurine.
   iii. Cholesterol $\rightarrow$ Coprosterol.

3. *Proteins* :
   i. Changes brought about on proteins are known as putrefaction.
   ii. Hydrolysis of protein
   iii. Further changes are deamination, decarboxi lation, oxidation, reduction and demethylation takes place on the liberated amino acids.

Table 10-10 *:* **Normal transport of substances by the intestine and location of maximum absorption or secretion.**[1]

Absorption of :	*Small Intestine*			*Colon*
	Upper[2]	*Mid*	*Lower*	
Sugars (glucose, galactose, etc)	++	+++	++	0
Amino acids	++	+++	++	*0*
Water-soluble and fat-soluble vitamins except vitamin B12	+++	++	0	0
Betaine, dimethylglycine, sarcosine	+	++	++	*?*
Antibodies in newborns	+	++	+++	?
Pyrimidines (thymine and uracil)	+	+	*?*	*?*
Fatty acid absorption and conversion to triglyceride	+++	++	+	0
Bile salts	+	+	+++	*0*
Vitamin B_{12}	0	+	+++	0
Na^{+}	+++	++	+++	+++
K^{+}	+	+	+	Sec
Ca^{++}	+++	++	+	*?*
Fe^{++}	+++	++	+	?
Cl^{-}	+++	++	+	+
SO_4^{++}	++	+	0	?

Ref. Ganong 22th Edition

Mastication

Definition : As soon as food is taken into the mouth, it is ground under the teeth by a process known as mastication of chewings.

Mechanism : It is due to alternate contraction and relaxation of the muscles concerned in the movement of lower jaw, aided by muscles of tongue, lips and cheks. It is a reffex act.

Steps : Mastication process consists of-

1. Crushing movement or biting with closed mouth (upward movement of the lower jaw) : Carried out by combined action of masseter, temporalis and pterygoids.
2. Opening of mouth (downward movement of lower jaw) : By digastrics and mylohyoids and help by gravity.
3. Rotatory movement of the molars : By pterygoids. It is essential for grinding.

   Apart from these, the jaw moves side to side and also forward and backward.

Purpose of mastication :

1. It helps in digestion.
2. It helps in swallowing.
3. During chewing, secretion of saliva helps dissolution of food materials, needed to stimulate taste sensation, so increases palatability of the food.
4. It imparts the sensation of pleasure in taking food and leads to satisfaction and contentment.
5. Prolonged chewing with pleasantness of taste leads to initiate the cephalic phase of digestive juice.

Deglutition or Swallowing

Definition : It is the process by which the bolus of food, formed during chewing is propelled backward and pass into stomach through oesophagus is called deglutition. It takes only 9 -12 seconds.

Mechenism : Swallowing (deglutition) is a reflex response that is triggered by afferent impulses in the trigeminal, glossopharyngeal, and vagus nerves. These impulses are integrated in the nucleus of the tractus solitarius and the nucleus ambiguus. The efferent fibers pass to the pharyngeal musculature and the tongue via the trigeminal, facial, and hypoglossal nerves. Swallowing as initiated by the voluntary action of collecting the oral contents on the tongue and propelling them backward into the pharynx. This starts a wave of involuntary contraction in the pharyngeal muscles that pushes the material into the esophagus. Inhibition of respiration and glottic closure are part of the reflex response. Swallowing is difficult if not impossible when the mouth is open, as anyone who has spent time in the dentist's chair feeling saliva collect in the throat is well aware. A normal adult swallows frequcntly while eating, but swallowing also continues between meals. The total number of swallows per day is about 600 : 200 while eating and drinking, 350 while awake without food, and 50 while sleeping.

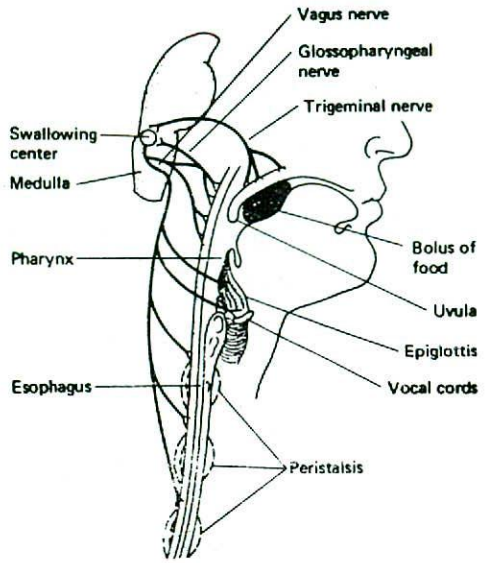


Fig. 10-11. *Mechanism of swallowing.*

At the pharyngoesophageal junction, there is a 3 cm segment of esophagus in which the resting wall tension is high. This segment relaxes reflexly upon swallowing, permitting the swallowed material to enter the body of the esophagus. A peristaltic ring contraction of the esophageal muscle forms behind the material, which is then swept down the esophagus at a speed of approximately 4 cm/s. When humans are in an upright position, liquids and semisolid foods generally fall by gravity to the lower esophagus ahead of the peristaltic wave.

(Ref. Ganong 22th Edition; page 489)

Low of gut

An electrical stimulus to any point of a gut causes a contractile ring to appear near the point of stimulus but at the same time causes a relaxation- receptive relaxation several cm down the gut towards the anus.

Movement of GI tract

Basic movement of GI tract

There are two basic type of movements :

1. Mixing movement.
2. Propulsive movement.

Mixing movement

i. *Definition* : It is the movement which mixes intestinal contents.

ii. *Type :* Fixed.

iii. *Pattern :* Contraction and relaxation.

iv. *Cause :*

   a. Peristaltic contraction.

b. Local constrictive contractions of small segment of gut wall.

v. *Purpose :*
   a. Mixes the food particles with digestive juices.
   b. Helps in absorption by constant bringing of chyme with absorptive surface.

Propulsive movement *(Peristalsis)*

i. *Definition* : It is the movement that propels intestinal content in aboral direction that is from mouth to anus.

ii. *Type :* Translatory; moves the food paticle anal wards.

iii. *Pattern :* Proximal contraction and distal relaxation.

iv. *Cause :* Distension of gut wall.

v. *Purpose :*
   a. To travel the food in aboral direction.
   b. Helps in the partial mixing of food with digestive juices.

Cause of anal ward movement

i. Receptive relaxation and low of gut

ii. Gradient theory for analward movement.

Movements of different part of GIT

1. *In stomach* :
   i. Mixing movement.
   ii. Propulsive or peristalsis movement.
   iii. Hunger contraction.
2. *In small intestine :*
   i. Mixing movement or segmentation (1 cm at a time).
   ii. Propulsive or peristalsis (velocity 0.5-2 cm/sec).
   iii. Pendular movement.
3. *In large intestine* :
   i. Mixing movement or Haustration (2.5 cm at a time)
   ii. Propulsive movement or Mass movement (20 cm at a time).
4. *Movement of villi* :
   i. Side to side movement
   ii. Pumping movement.

Segmentation contraction *(mixing contractions)*

When a portion of the small intestine becomes distended with chyme, the stretching of the intestinal wall elicits localized concentric contractions spaced at intervals along the intestine and lasting a fraction of a minute. The contractions cause 'segmentation' of the samll intestine. That is they divide the intestine into spaced segments that have the appearance of a chain of sausages. As one set of segmentation contractions relaxes, a new set often begins, but the contractions this time occur mainly at new points between the previous contrctions. Therefore, it is clear that the segmentation contractions can 'chop' the chyme about 2 to 3 times per minute, in this way promoting progressive mixing of the solid food paticles with the secretions of the small intestine. This frequency is about 12 per minute in the duodenum, and proximal jejunum, the maximum

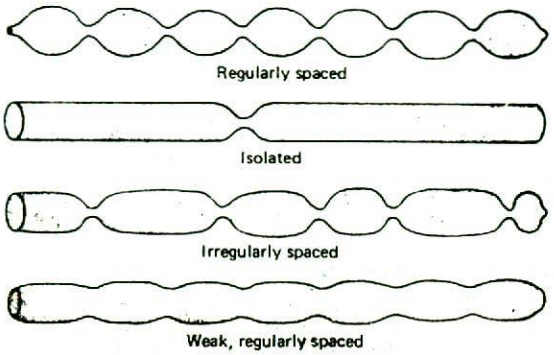


Fig. 10-12. *Segmentation contraction.*

frequency of the segmentation contractions in these areas is also about 12 per minute. However, in the terminal ileum, the maximum frequency is usually 8 to 9 contractions per minute.

The segmentation contractions become exceedingly weak when the excitatory activity of the enteric nervoous system is blocked by atropine.

(Ref. Guyton & Hall-11th Edition, Page 787)

Propulsive or peristalsis movement

Peristalsis in the small intestine : Chyme is propelled through the small instestine by peristatic waves. These can occur in any part of the small intestine, and they move anal ward at a velocity of 0.5 to 2 cm per second, much faster in the proximal intestine and much slower in the terminal intestine. However, they are normally very weak and usually die out after travelling only 3 to 5 cms, very rarely farther than 10 cms, so that the movement of the chyme is also very slow, so slow in fact that the net movement of the chyme along the small intestine averages only 1 cm per minute. This means that normally 3 to 5 hours are required for passage of chyme from the pylorus to the ileocecal valve.

Control of peristalsis by nervous and hormonal signals : Peristaltic activity of the small intestine is greatly increased after a meal. This is caused partly by the beginning entry of chyme into the duodenum but also by the so called gastroenteric reflex that is initiated by distension of the stomach and conducted principally through the myenteric plexus from the stomach down along the wall of the small intestine. This reflex increases the over all degree of excitability of the small intestine, including both increased motility and secretion. The function of the peristaltic waves in the small intestine is not only to cause progression of the chyme toward the ileocecal valve but also to spread out the chyme along the intestinal mucosa.

(Ref. Guyton 10th Edition, Page-734)

The peristaltic rush : Though peristalsis in the small intestine

is normally very weak, intense irritation of the intestinal mucosa, as occurs in some severe cases of infectious diarrhoea, can cause both very powerful and rapid peristalsis called the *peristaltic rush*. This is initiated mainly by extrinsic nervous reflexes to the brain stem and back again to the gut. The powerful peristaltic contractions then tavel long distances in the small intestine within minutes, sweeping the contents of the intestine into the colon and thereby relieving the small intestine of either irritative chyme or excessive distension.

(Ref. Guyton & Hall-11th Edition, Page 787)

Movements of the colon

1. ***Haustrations** (Mixing movements)* : It is the mixing movement of large intenstine. At each saculation of large intenstine, the circular muscles contract first and constricting the lumen of the colon almost to occlusion. This is immediately followed by the contraction of the longitudinal muscles which are aggregated to form three longitudinal strips known as *taenia coli*. These combined contraction of the circular and longitudinal muscles cause the unstimulated portion of the large intestine to bulge outward into bag like sacs called haustrations.

   In this movement all the faecal materials is gradually exposed to the surface of the large intestine and fluid is progressively absorbed.

   (Ref. Guyton & Hall-11th Edition, Page 788)

2. ***Mass Movements** (propulsive movements)* : A mass movement is a modified type of peristalsis characterized by the following sequence of events :
   i. *First*, a constrictive ring occurs in response to a distended or irritated point in the colon, usually in the transverse colon.
   ii. Then, rapidly thereafter the 20 or more centimeters of colon distal to the constriction lose their haustrations and instead contract as a unit, forcing the fecal material in this segment en masse further down the colon. The contraction develops progressively more force for about 30 seconds, and relaxation then occurs during the next 2 to 3 minutes. Then, another mass movement occurs, this time perhaps farther along the colon.

   A whole series of mass movements usually persists for 10 to 30 minutes. Then they cease but return perhaps a half day or even a day later. When they have forced a mass of feces into the rectum, the desire for defecation is felt.

   Initiation of mass movements by gastrocolic and duodenocolic reflexes : The appearance of mass movements after meals is facilitated by gastrocolic and duodenocolic reflexes. These reflexes result from distention of the stomach and duodenum. They occur either not at all or hardly at all when the extrinsic autonomic nerves to the colon have been removed; therefore, the reflexes almost certainly are initiated by way of the autonomic nervous system.

   Irritation in the colon can also initiate intense mass movements. For instance, a person who has an ulcerated condition of the colon mucosa (*ulcerative colitis*) frequently has mass movements that persist almost all the time.

   (Ref. Guyton & Hall-11th Edition, Page 789)

Pyloric pump : The pumping action of the antral portion of stomach that propels chyme from stomach to duodenum is called pyloric pump.

Kneading movements : These are contractions affecting a large segment with relaxation of the adjacent segment, which go on alternately shaking the content vigorously.

Antiperistaltic movements : It is the reverse peristalsis occurs in a part of the large intestine, especially in ascending and transverse colon. This usually alternates with normal peristalsis, so the contents have no chance to be moved into aboral direction. This movement prolongs the stay of the contents to help absorption of water. It is rarely seen in human beings.

Hunger : It is the some total of those process which leads to intake of food. Lateral nucli of hypothalamus acts as hunger centre.

Appetite : A desire to take a particular type of food.

Hunger pangs : When hunger contraction actually causes pain in stomach pit then it is called hunger pangs. Usually do not begins 12 to 24 hours after the last ingestion of food.

Hungar contraction : Beside the peristaltic contraction that occur when food is present in the stomach, another type of intense contraction, called hungar contraction, often occurs when the stomach has been empty for several hours or more.

(Ref. Guyton & Hall-11th Edition, Page 785)

Vomiting

a. *Definition* : It is the process by which the content of upper gastro intestinal tract is expelled out through mouth cavity.

b. *Cause :*
   i. It is due to irritation, distention or over excitation of stomach or doudenum.
   ii. Vomitting may also caused by stimulation of chemoreceptor trigger zone of medulla by some drugs (apomorphine, morphine) or by motion sicknes. It may also occur due to cortical excitation.

c. *Mechanism of vomitting :*
   i. A deep breath.
   ii. Rising of hyoid bone and larynx to pull the

cricoesophageal sphincture open.

iii. Closing of glotis.

iv. Lifting the soft palate to close the posterior naris.

v. Strong downward contraction of the diaphragm along with the simultaneous contaction of all the abdominal muscles & squeezing the stomach & rise of intragastric pressure.

vi. Relaxation of gastro-oesophageal sphincture and finally expulsion of gastric content.

Feces

Approximate composition of feces on an average diet

Component	*Percentage of total Weight*
Water	75
Solids	25
	Percentage of total Solids
Cellulose and other indigestible fiber	Variable
Bacteria	30
Inorganic material (mostly calcium andphosphates)	15
Fat and fat derivatives	5

Also desquamated mucosal cells, mucus and small amounts of digestive enzymes.

(Ref. Ganong 22th edition, Page 509)

Defecation

Most of the time, the rectum is empty of feces. This results partly from the fact that a weak functional sphincter exists about 20 centimeters from the anus at the juncture between the sigmoid colon and the rectum. There is also a sharp angulation here that contributes additonal resistance to filling of the rectum. When a mass movement forces feces into the rectum, the desire for defecation is normally initiated immediately, including reflex contraction of the rectum and relaxation of the anal sphincters.

Continual dribble of fecal matter through the anus is prevented by tonic constriction of-

i. The *internal anal sphincter*, a several-centimeters-long thickening of the circular smooth muscle that lies immediately inside the anus.

ii. The *external anal sphincter*, composed of striated voluntary muscle that both surrounds the internal sphincter and extends distal to it. The external sphincter is controlled by nerve fibers in the pudendal nerve, which is part of the somatic nervous system and therefore is under *voluntary, conscious* or at least *subconscious control*; subconsciously, it is usually kept continuously constricted unless conscious signals inhibit the constriction.

Defecation reflexes : Ordinarily, defecation is initiated by defecation reflexes.

1. *Intrinsic reflex* : One of these reflexes is an *intrinsic reflex* mediated by the local enteric nervous system in the rectal wall. This can be described as follows :

   When feces enter the rectum, distention of the rectal wall initiates afferent signals that spread through the myenteric plexus to initiate peristaltic waves in the descending colon, sigmoid, and rectum, forcing feces toward the anus. As the peristaltic wave approaches the anus, the internal anal sphincter is relaxed by inhibitory signals from the myenteric plexus; if the external anal sphincter is also consciously, voluntarily relaxed at the same time, defecation occurs.

   However, the intrinsic myenteric defecation reflex functioning by itself is relatively weak. To be effective in causing defecation, it usually must be fortified by another type of defecation reflex, a parasympathetic defecation reflex.

ii. *Parasympathetic defecation reflex* : It involves the sacral segments of the spinal cord. When the nerve endings in the rectum are stimulated, signals are transmitted first into the spinal cord and then reflexly back to the descending colon, sigmoid, rectum, and anus by way of parasympathetic nerve fibers in the pelvic nerves. These parasympathetic signals greatly intensify the penstaltic waves as well as relax the internal anal sphincter and thus convert the intrinsic myenteric defecation reflex from a weak effort into a powerful process of defecation that is sometimes effective in emptying the large bowel all at once all the way from the splenic flexure of the colon to the anus.

iii. Also, the afferent defecation signals entering the spinal cord initiate other effects, such as taking a deep breath, closure of the glottis, and contraction of the abdominal wall muscles to force the fecal contents of the colon downward and at the same time cause the pelvic floor to relax downward and pull outward on the anal ring to evaginate the feces.

(Ref. Guyton & Hall-11th Edition, Page 789)

Constipation

i. *Definition* : Constipation means slow movement of feces through the large intestine; it is often associated with large quantities of dry, hard feces in the descending colon that accumulate because of the long time available for absorption of fluid.

ii. *Cause* :

   a. Any pathology of the intestines that obstructs movement of intestinal contents, such as tumors, adhesions that constrict the intestines, and ulcers, can cause constipation.

b. A frequent functional cause of constipation is irregular bowel habits that have developed through a lifetime of inhibition of the normal defecation reflexes.
c. Infants are seldom constipated but part of their training in the early years of life requires that they learn to control defecation, and this control is effected by inhibiting the natural defecation reflexes.
d. Clinical experience shows that if one fails to allow defecation to occur when the defecation reflexes are excited or if one overuses laxatives to take the place of natural bowel function, the reflexes themselves become progressively less strong over a period of time and the colon becomes atonic.
e. Constipation can also result from spasm of a small segment of the sigmoid colon. It should be recalled that motility even normally is weak in the large intestine, so that even a slight degree of spasm is often capable of causing serious constipation.

iii. *Effects* : After the constipation has continued for several days and excessive feces have accumulated above the spastic sigmoid colon, excessive colonic secretions often lead to a day or so of diarrhoea. After this, the cycle begins again, with repeated bouts of alternating constipation and diarrhoea.

iv. *Management* :
a. Establishment of regular bowel habits early in life, usually defecating in the morning after breakfast when the gastrocolic and duodenocolic reflexes cause mass movements in the large intestine, the development of constipation in later life can generally be prevented.
b. Laxatives.

(Ref. Guyton & Hall-11th Edition; page 822)

(Q. 10. Write short notes on- constipation)

Flatus

i. *Definition* : Gases in the gastrointestinal tract called *flatus*.

ii. Sources : Gases, called flatus, can enter the gastrointestinal tract from three sources :
a. Swallowed air
b. Gases formed as a result of bacterial action
c. Gases that diffuse from the blood into the gastrointestinal tract.

iii. *Composition* :
a. *In the stomach* : Most gases in the stomach are mixtures of nitrogen and oxygen derived from swallowed air, and in the typical person most of these gases are expelled by belching.
b. *In the small intestine* :
* Only small amounts of gas are normally present in the small intestine, and much of this *gas is air* that passes from the stomach into the intestinal tract.
* In addition, considerable amounts of *carbon dioxide* occasionally accumulate because reaction between acidic gastric juice and bicarbonate in pancreatic juice sometimes liberates carbon dioxide too rapidly for all of this to be absorbed.

c. *In the large intestine* :
* A greater proportion of the gases is derived from *bacterial action*, including especially *carbon dioxide*, *methane* and *hydrogen*. They occur along with varying amounts of oxygen and nitrogen from swallowed air.
* When the methane and hydrogen become suitably mixed with oxygen from swallowed air, an actual *explosive mixture* is rarely formed; use of the electric cautery during sigmoidoscopy has been known to cause a mild explosion.

iv. *Foods cause greater expulsion of flatus* : Certain foods are known to cause greater expulsion of flatus through the anus than others- *beans, cabbage, onion, cauliflower, corn*, and *certain irritant foods such as vinegar.*

Some of these foods serve as a suitable medium for gas-forming bacteria, especially because of unabsorbed fermentable types of carbohydrates (for instance, beans contain an undigestible sugar that passes into the colon and becomes a superior food for the colonic bacteria. But in other instances, excess expulsion of gas results from irritation of the large intestine, which promotes rapid peristaltic expulsion of gases before they can be absorbed.

v. *Amount of gas formation* : The amount of gases entering or forming in the large intestine each day averages 7 to 10 liters.

vi. *Amount of gas expulsion and absorption* : The amount expelled through the anus is usually only liter. The remainder is normally absorbed into through the intestinal mucosa and expelled into the lung.

(Ref. Guyton & Hall-11th Edition; page 825)

(Q. 10. Write short notes on- Flatus)

Lactose intolerance

In most mammals and in many races of humans, *intestinal lactase* activity is high at birth, then declines to low levels during childhood and adulthood. The low lactase levels are associated with intolerance to milk (*lactse intolerance*).

Milk intolerance can be ameliorated by administration of commercial lactase preparations, but this is expensive. Yogurt is better tolerated than milk in intolerant individuals because it contains its own bacterial lactase.

(Ref. Ganong 22th Edition; page 469)

(Q. 09. Write short notes on- Lactose intolerance)

Introduction 10.35
Gastric juice & Enzymes 10.36
Saliva 10.36
Gastric juice 10.37
Pancreatic juice 10.37
Small intestinal enzymes 10.37
Gastro-intestinal hormones 10.38
Hepato-billiary system 10.40
Digestion and absorption 10.41
Regulation of GIT activities10.42
Movements of GIT 10.44
Applied 10.45

***Direction** : Write T for true & F for false against each of the following statement.*

Introduction

Q. 01. **Substances having antioxidant effects are**
- T a. vitamin E
- T b. selenium
- T c. vitamin A
- F d. vitamin K
- F e. thiamin.

Q. 02. **Function of the gastrointestinal tract are**
- T a. nervous and hormonal control.
- T b. absorption of digestive products
- T c. propultion of food through alimentary tract
- F d. absorption of digestive juice
- F e. circulation of hormone

Q. 03. **Regarding gastorintestinal blood flow**
- T a. PO_2 is high in the venules
- T b. it is increased by bradykinin
- T c. it is decreased by sympathetic stimulation.
- F d. PO_2 is high in the tips of the villi
- F e. it is increased by gastrin.

Q. 04. **Gastrointestinal smooth muscle**
- T e. spike potentials last for 10 to 20 milli seconds
- T a. functions as a syncytium
- T b. contracts rhythmically
- F c. spike potentials are not true action potentials
- F d. action potential are same as nerve fibers

Q. 05. **Salivary glands are activator of**
- T a. Cl^-
- F b. HCl
- F c. trypsin
- F d. enteropeptidase
- F e. H^+.

Q. 06. **Digestive activities of the pharynx are**
- T a. deglutition
- T b. closing the airway passage
- F c. relaxation of upper esophageal sphincter
- F d. permitting entry of bolus into stomach
- F e. lubrication of esophagus.

Q. 07. **Regarding stomach**
- T a. here HCl reduces ferric irons to ferrous irons.
- T b. motility is inhibited by enterogastrone
- F c. motility is increased when fats enter duodenum
- F d. absorbs vitamin B_{12}
- F e. secretion is inhibited by pentagastrin.

Q. 08. **Stomach**
- T a. stores food.
- T b. mixes food and gastric juice
- T c. secretes gastric juice
- F d. completes the digestion of proteins
- F e. absorbs 90% of all nutrients

Q. 09. **In the colon**
- T a. fecal transit time is inversely related to its fiber content
- T b. water absorbtion is more than in the small intestine
- T c. mucus lubricate the fecal contents
- F d. fecal transit time is about 7 days
- F e. bacteria amount to three quarters of the fecal weight.

Q. 10. **Appetite for food is increased**
- T a. if blood glucose level falls
- T b. by the type of food.
- T c. when lateral hypothalamic area is stimulated
- F d. if the stomach is distended
- F e. if posterior hypothalamic area is stimulated.

Q. 11. **Thirst sensation**
- T c. may be produced on stimulation of hypothalamus
- T d. is produced by rise in osmolarity of body fluid
- T a. increases in severe dehydration
- F b. decreases in severe dehydration
- F e. is produced by rise in blood volume.

Q. 12. **Dietary fiber includes one of following**
- T b. Pectins
- F a. Collagen
- F c. Keratin

F d. Elastin
F b. All.

Q. 13. **An increase in body fat increase**
T a. probability of increased morbidity and premature mortality.
T b. survival time during fasting
T c. survival time in cold weather
F d. percentage of water in the body
F e. specific gravity of the body

Q. 14. **Which of the following does not change with age**
T a. Glucose tolerance
F b. FEV_1
F c. GFR
F d. Hematocrit
F e. All.

Q. 15. **Energy for the brain in starvation is from**
T a. Glucose
T b. Ketones
F c. Fatty acids
F d. Amino acids
F e. All.

Gastric juice & Enzymes

Q. 16. **The feature of enzyme cascade systems is**
T a. Feed back regulation
F b. Amplification
F c. Allostearic inhibition
F d. Counter regulation
F e. None.

Q. 17. **Fastest acting enzyme is**
T a. Carbonic anhydrase
F b. Pepsin
F c. Trypsin
F d. Thrombin
F e. None.

Q. 18. **Mucus is secreted by**
T a. stomach
T b. duodenum
T c. ileum
T d. large intestine
F e. ear.

Saliva

Q. 19. **Saliva**
T a. contains high concentrations of potassumand bicarbonate ions.
T b. lubricates the mouth
T c. has antiseptic action
T d. helps in speech
F e. is required for complete digestion of starch

Q. 20. **Salivary secretion**
T a. contains low concentrations of sodium and chloride ions
T b. can be affected by higher centers.
F c. is decreased by parasympathetic stimulation
F d. is primarily under hormonal control
F e. increases during nervousness

Q. 21. **Saliva plays important role in**
T a. prevention of dental carries
T b. buffering action
T c. deglutition
F d. excretion of ammonia and salt
F e. water balance

Q. 22. **Characteristics of saliva include**
T a. more than twice the iodide level of plasma
F b. similar composition from different salivary gland.
F c. has no enzymic content
F d. less than half the ionic calcium level of plasma
F e. pH between 5 and 6.

Q. 23. **Saliva is necessary for**
T a. digestion of food
T b. swallowing of food
T c. taste sensation
T d. heat loss
T e. bacteriolytic action.

Q. 24. **The major enzyme of saliva is**
T a. amylase
F b. trypsin
F c. lipase
F d. pepsin
F e. gastrin.

Q. 25. **Hyposalivation occurs in**
T a. fever.
T b. sialolithiasis
T c. emotional state
F d. neoplasm of mouth
F e. pregnancy

Q. 26. **Hypersalivation occurs in**
T a. neurological disorder
T b. ulceration of esophagus
T c. pregnancy
F d. emotional state
F e. fever.

Q. 27. **Salivary secretions are abolished**
- T a. by the administration of anticholinergic agents
- F b. by activation of the sympathetic nerve
- F c. when weak acid are present in the mouth
- F d. at the one set of vomiting
- F e. by thinking of appetizing food.

Gastric juice

Q. 28. **Gastric hydrocholoric acid**
- T a. denatures proteins
- T b. sitmulates secretion of CCK
- T c. inhibits secretion of gastrin.
- F d. stimulates secretion of gastrin
- F e. inhibits secretion of secretin.

Q. 29. **Regarding reaction of digestive juices**
- T a. saliva usually slightly acidic
- T b. pancreatic juice alkaline
- F c. intestinal juice strongly alkaline
- F d. intestinal juice strongly acidic
- F e. gastric juice slightly acidic.

Q. 30. **The chief cells of the oxyntic glands**
- T a. secrete gelatinase.
- T b. are basophilic
- T c. secrete pepsinogen
- F d. secrete muc in
- F e. secrete HCI

Q. 31. **Pyloric glands of stomach secretes**
- T a. gastrin.
- T b. thick alkaline viscid mucous
- F c. both acid and pepsin
- F d. small amount of pepsinogen
- F e. alkaline thin watery mucus

Q. 32. **Which inhibits gastric secretion?**
- T a. Secretin
- F b. High gastric pH
- F c. Calcium
- F d. Insulin
- F e. All.

Q. 33. **Pepsin is an example of**
- T a. enzyme
- F b. hormone
- F c. nutrient
- F d. vitamin
- F e. lipid.

Q. 34. **Pepsin**
- T a. breaks certain peptide bonds
- T b. is the active form of pepsinogen
- F c. is secreted from zymogenic cells
- F d. splits short chain of triglycerides
- F e. kills microbes in a food.

Q. 35. **Pepsinogen is activated by**
- T a. Low pH
- F b. Enterokinase
- F c. Trypsin
- F d. Chymotrypsin
- F e. All.

Pancreatic juice

Q. 36. **Pancreatic secretion contain**
- T a. Trypsin
- T b. Lipase
- F c. Enteropeptidase
- F d. Pepsin
- F e. Renin

Q. 37. **Severe exocrine pancreatic deficiency causes**
- T a. undigested muscle fibres in the stool
- T b. bleeding tendency
- T c. steatorrhea
- F d. an abnormal mucous in the small intestine
- F e. normal glucose tolerance test

Q. 38. **Islets of Langerhans are found in**
- T a. pancreas
- F b. ovary
- F c. spleen
- F d. brain
- F e. liver.

Q. 39. **Pancreatic juice rich in water and electrolytes but poor in enzymes is secreted in response to**
- T a. Secretin
- F b. Pancreatozymin
- F c. Cholecystokinin
- F d. Proteins
- F e. All.

Small intestinal enzymes

Q. 40. **The brush border enzymes are**
- T a. invertase.
- T b. lactase
- T c. aminopeptidase
- F d. nuclease
- F e. chollagenase

Q. 41. **Small intestinal enzymes are**
- T a. enterokinase.
- T b. α-dextrinase

T c. maltase
F d. ribonuclease
F e. lipase

Q. 42. **Trypsinogen**
T a. is converted to trypsin by enterokinase
T b. remains as trypsinogen by trypsin inhibitor
T c. is secreted during cephalic phase of digestion.
T d. is the inactive form of trypsin
F e. is converted to trypsin by HCl

Q. 43. **Chymotrypsinogen is activated into chyrnotrypsin by**
T a. Trypsin
F b. Pepsin
F c. Fatty acids
F d. Bile salts
F e. All.

Q. 44. **Succus entericus is secreted by**
T a. crypts of leiberkuhn and brunner's gland
F b. islets of langerhans
F c. gastric glands
F d. goblet cell
F e. salivary glands.

Q. 45. **The following are decreased in proenzyme form**
T a. Trypsin
T b. Chymotrypsin
T c. Pepsin
F d. Ribonuclease
F e. All.

Q. 46. **Which secretion contributes to the maximum amount of potassium**
T a. Salivary
F b. Gastric
F c. Pancreatic
F d. Biliary
F e. None.

Q. 47. **The rate of basic electrical rhythm (BER) is high in**
T a. duodenum
F b. stomach
F c. jejunum
F d. ileum
F e. colon.

Gastro-intestinal hormones

Q. 48. **Following are local hormones**
F a. Insulin
T b. Heparin
T c. Bradykinin
T d. Acetyl choline
F e. All

Q. 49. **Following are gastrointestinal hormones**
T a. CCK - PZ
T b. GIP
T c. Motilin
F d. Chymotrypsin.
F e. All

Q. 50. **Following are gastrointèstinal hormones except**
F a. CCK - PZ
F b. GIP
F c. Motilin
T d. Chymotrypsin.

Q. 51. **Gastrointestinal hormones are**
T a. motilin
T b. CCK
T c. GIP
F d. enterokinase
F e. histamine

Q. 52. **The hormone mainly acting on stomach is**
T a. gastrin
T b. bombesin
F c. pancreozymin
F d. secretin
F e. VIP.

Q. 53. **The duodenum secretes a hormone which has following effects except**
T b. Increases gastric motility
F a. Causes copious pancretic juice rich in bicarbonate and poor in enzymes
F c. Causes gall bladder to contract and sphincter of Oddi to relax
F d. Leads to meagre flow of pancreatic juice rich in enzymes
F e. None.

Q. 54. **The duodenum secretes a hormone which has following effects**
T a. Causes gall bladder to contract and sphincter of Oddi to relax
T b. Leads to meagre flow of pancreatic juice rich in enzymes
T c. Causes copious pancretic juice rich in bicarbonate and poor in enzymes
F d. Increases gastric motility
F e. All.

Q. 55. **Gastrin secretion is inhibited by**
T a. luminal acid
T b. somatostatin

T c. calcitonin.
F d. luminal distention
F e. peptides and amino acid

Q. 56. **Gastrin secretion**
T a. is enhanced by mere thought of food
T b. is stimulated by histamine secretion.
T c. contains factor which helps in vit B_{12} absorption.
F b. is decreased by eating food
F e. is stimulated by pancreozymin.

Q. 57. **Stimuli that increase gastrin secretion are**
T a. increased vagal discharge
T b. luminal peptides and aminoacid
T c. blood borne calcium and epinephrine
F d. somatostatin
F e. secretin

Q. 58. **Gastrin**
T a. promotes secretion of gastric juice
T b. increases gastric motility
T c. promotes growth of gastric mucosa
F d. stimulates release of insulin
F e. slows gastric emptying.

Q. 59. **Gastrin**
T a. causes contraction of lower esophageal sphincter
T b. inereases motility of the stomach
F c. inhibits parietal cells to secrete HC1
F d. inhibits chief cells to secrete pepsinogen
F e. causes contraction of pyloric sphincter.

Q. 60. **Gastrin secretion is**
T c. Increased by stomach distention
F a. Inhibited by curare
F b. Stimulated by nor adrenaline
F d. Stimulated by an increase in tonic activity
F a. None.

Q. 61. **Gastrin is produced by**
T a. Pancreas
T b. Gastricantral cells
T c. Pituitary
T d. All
F e. None.

Q. 62. **Gastrin secretion is stimulated by the following**
T a. Gastric distension
T b. Gastrin
T c. Vagal stimulus
F d. Secretin
F e. None.

Q. 63. **Secretin does not cause**
T a. Gastric secretion increase
F b. Bicarbonate secretion
F c. Auguments the action of CCK
F d. Contraction of pyloric sphincter
F e. None.

Q. 64. **Secretin cause**
T a. Bicarbonate secretion
T b. Auguments the action of CCK
T c. Contraction of pyloric sphincter
F d. Gastric secretion increase
F e. All

Q. 65. **Secretin**
T a. stimulates secretion of bile.
T b. inhibits secretion of gastric juice
T c. promotes normal growth and maintenance of pancreas
F d. inhibits secretion of pancreatic juice
F e. decreases effects of CCK

Q. 66. **Intrinsic factor**
T a. is secreted from oxyntic cells.
T b. is needed for absorption of vitamin B_{12}
T c. is required for erythropoiesis
F d. forms a protective barrier
F e. prevents digestion of stomach wall

Q. 67. **Cholecystokinin**
T a. causes ejection of bile from gallbladder
T b. causes opening of sphincter of oddi
T c. induces satiety
F d. stimulates gastric emptying
F e. decreases effects of secretin.

Q.68. **Gastric inhibitory peptides**
T a. inhibits sceretion of gastric juice
T b. slows gastric emptying
T c. stimulates release of insulin by pancreatic beta cells
F d. stimulate sceretion of gastric juice
F e. promotes gastric emptying.

Q. 69. **Actions of cholecystokinin include the following**
T a. Contraction of gall bladder
T b. Secretion of pancreatic juice rich in enzymes
T c. Increases the secretion of enterokinase
T d. Augments the action of secretion of gastrin
F e. Stimulated gastric emptying.

Q. 70. **Actions of cholecystokinin include all of the following except**
T e. Stimulated gastric emptying.
F a. Contraction of gall bladder
F b. Secretion of pancreatic juice rich in enzymes
F c. Increases the secretion of enterokinase
F d. Augments the action of secretion of gastrin

Q. 71. **D cells of pancreas secrete**
- T a. Somatostatin.
- F b. Insulin
- F c. Glucagon
- F d. VIP
- F e. None.

Hepato-billiary system

Q. 72. **Bile enters the gall bladder through the**
- T a. cystic duct
- F b. hepatie duct
- F c. common bile duct
- F d. thoracic duct
- F e. hepatopanereatic duct

Q. 73. **The liver stores**
- T a. glycogen
- T b. vitamin A
- F c. glucose
- F d. vitamin B_1, B_2, B_6 and C
- F e. bile salt.

Q. 74. **Bile is formed at the rate of how many ml/hour in liver**
- T a. 20
- F b. 40
- F c. 80
- F d. 100
- F c. 60.

Q. 75. **Maximum absorption of bile occurs at**
- T c. Ileum
- F a. Jejunum
- F b. Duodenum
- F d. Colon
- F c. Caecum.

Q. 76. **Liver is the only organ which normally**
- T a. Synthesizes heparin
- T b. Synthesizes urea
- T c. Degrades haemoglobin
- T d. Converts glycogen to glucose
- T e. All of the above.

Q. 77. **Most potent simulus for bile secretion is**
- T a. Bile salt
- F b. Cholecystokinin
- F c. Gastrin
- F d. Secretin
- F e. Bile acid

Q. 78. **Factors causing contraction of gall bladder include**
- T a. acetylcholine
- T b. fat in the small gut
- T c. CCK
- F d. Secretin
- F e. protein in the small gut.

Q. 79. **The liver is the principal site for**
- T a. storage of iron.
- T b. synthesis of plasma albumin
- F c. synthesis of plasma globulins
- F d. synthesis of vitamin B_{12}
- F e. storage of vitamin C

Q. 80. **Bile salts**
- T a. are derived from cholesterol
- T b. are essential for fat digestion
- T c. form micelles
- F d. are absorbed mainly in the upper small intestine
- F e. inhibit bile secretion by the liver.

Q. 81. **The liver**
- T a. inactivates gonadal steroid hormones.
- T b. maintains the normal blood glucose level
- T c. converts the NH_4 into urea.
- F d. synthesizes vitamin D_3.
- F e. manufactures immunoglobulins

Q. 82. **Urobilinogen is**
- T a. absorbed from the intestine
- T b. present in both urine and faeces.
- T c. excreated in bile
- F d. formed mostly in reticuloendothelial system
- F e. excreted mainly in the unne

Q. 83. **Enterohepatic circulation**
- T a. means recirculation of bile salt.
- T b. helps in conservation of bile salts
- F c. helps in excretion of bile salts
- F d. stimulates bile salt production in the liver
- F e. cause excreation of bile

Q. 84. **Bile salts assist in digestion of fats by**
- T a. breaking them into small fragement.
- T b. emulsification
- F c. contributing as lipolytic enzyme
- F d. stimulating secretion of a lipase
- F e. increasing the alkalinity of digestive medium

Q. 85. **Endogenous compounds excreted by the liver into the bile ducts are**
- T a. bile salt
- T b. cholesterol
- F c. albumin
- F d. ampicillin
- F e. sulfonamides.

Q. 86. **Exogenous compounds excreted by the liver are**
- T a. ampicillin
- T b. tetracycline.
- F c. urobilinogen
- F d. bilirubin
- F e. lecithin

Q. 87. **Hepatic protein synthesis leads to the production of**
- T a. albumin.
- T b. transport proteins
- T c. clotting factors
- F d. cholesterol
- F e. ketone bodies

Q. 88. **Lipid metabolic function of the liver results in**
- T a. synthesis of cholesterol
- T b. production of ketone bodies
- T c. excretion of cholesterol.
- F d. synthesis of clotting factors
- F e. synthesis of bile salts

Q. 89. **Composition of bile have**
- T a. sodium
- T b. potassium
- F c. magnesium
- F d. mucin
- F e. carbonic anhydrase.

Q. 90. **Lipoproteins are**
- T a. chylomicrons
- T b. VLDL
- T c. LDL
- T d. HDL
- F e. lacteal.

Digestion and absorption

Q. 91. **Digestion is chemically**
- T a. hydrolysis
- F b. hydrogenation
- F c. hydration
- F d. dehydration
- F e. condensation.

Q. 92. **Micelle formation is necessary for the intestinal absorption of**
- T a. vitamin D
- T b. fatty acids
- F c. bile acids
- F d. vitamin B_{12}
- F e. glycerol.

Q. 93. **Digestion of starch starts from**
- T a. mouth
- F b. esophagus
- F c. stomach
- F d. duodenum
- F e. jejunum.

Q. 94. **Intestinal absorption is faster for**
- T a. Hexoses
- F b. Dissacharides
- F c. Oligosaccharides
- F d. Polysaccharides
- F e. None.

Q. 95. **The final sugars in intestinal chyme are**
- T a. Glucose & fructose
- F b. Ribose & mannose
- F c. Ribose & xylulose
- F d. Xylulose & fructose
- F e. None.

Q. 96. **The only sugar normally absorbed in the intestine against a concentration gradient is**
- T a. Glucose
- F b. Xylose
- F c. Mannose
- F d. Ribose
- F e. Galactose.

Q. 97. **Active reabsorption of glucose occurs in the**
- T a. Proximal tubule
- F b. Distal tubule
- F c. Loop of henle
- F d. Collecting ducts
- F e. None.

Q. 98. **Gastric digestion is most important for**
- T a. proteins
- F b. fats
- F c. carbohydrates
- F d. vitamins
- F e. minerals.

Q. 99. **Fat absorption occurs in the**
- T a. duodenum
- T b. ileum
- F c. stomach
- F d. colon
- F e. rectum.

Q. 100. **Short chain fatty acid produced by bacteria are maximally absorbed in**
- T a. Colon
- F b. Duodenum
- F c. Ileum

F d. Jejunum
F d. Stomach.

Q. 101. **Fat is maximally absorbed in**
T a. Jejunum
F b. Ileum
F c. Colon
F d. Stomach
F e. Duodenum

Q. 102. **Elimination of terminal ileum is associated with malabsorption of**
T a. vitamin B_{12}
T b. fats
F c. protein
F d. carbohydrate
F e. vitamin C.

Q. 103. **Chylomicrons**
T a. supply dietary lipid to cell
T b. are lipid carrier proteins
F c. are originated from liver
F d. carry dietary protein
F e. deliver endogenous triglyceride to cell.

Q. 104. **Ingested vitamin B_{12}**
T a. is bound to protein R
T b. forms B_{12} intrinsic factor complex
T c. binds to parietal cells.
T d. binds to intrinsic factor in the stomach
F e. is absorbed in the stomach

Q. 105. **Physiology of digestion in large intestine include**
T a. synthesis of some vitamins
T b. chemical digestion through bacterial action.
F c. chylomicrons move into lymph
F d. chylomicrons are synthesized to triglycerides
F e. formation of chylomicrons

Q. 106. **Elimination of terminal ileum is associated with malabsorption of**
T a. vitamin B_{12}
T b. fats
F c. protein
F d. carbohydrate
F e. vitamin C.

Q. 107. **Potassium content in colonic secretion is**
T a. 30 meq/L
F b. 10 meq/L
F c. 15 meq/L
F d. 50 meq/L
F e. 45 meq/L.

Q. 108. **Which of the following is absorbed in the colon**
T a. Electrolytes
F b. Iron
F c. Proteins
F d. Bile salts
F e. Glucose.

Q. 109. **Which of the following is absorbed in the proximal intestine**
T a. Iron
F b. Electrolytes
F c. Bile salts
F d. Vitamin B_{12}
F e. Proteins

Q. 110. **Which of the following is the fastest to be absorbed from the stomach**
T a. Water
F b. Carbohydrate
F c. Proteins
F d. Fats
F e. Bile salts

Q. 111. **Which secretion contributes to the maximu amount of potassium**
T a. Salivary
F b. Gastric
F c. Pancreatic
F d. Intestinal
F e. Biliary.

Regulation of GIT activities

Q. 112. **Swallowing centre is situated in**
T a. Medulla
F b. Midbrain
F c. Pons
F d. Cerebellum
F e. Spinal cord.

Q. 113. **Satiety centre in hypothalamus is regulated by**
T a. Blood glucose levels
F b. Gastric dilatation
F c. All of the above
F d. Blood insulin levels
F e. None.

Q. 114. **Anabolic action on protein is mediated by**
T a. Testesterone
F b. ACTH
F c. Insulin
F d. TSH
F e. None.

Q. 115. **Vagal stimulation following intake of food affect the secretion of**
T a. Stomach
T b. Pancreas

T c. Gall bladder
F d. Parotid
F e. All.

Q. 116. **Vagal stimulation cause the following**
T a. Increase in intestinal secretion
T b. Constriction of intestinal musculature
T c. Fall in blood pressure
F d. Relaxation of bronchial musculature
F e. None.

Q. 117. **Vaso-vagal reflex is most dependent on**
T a. receptive relaxation
T b. gastric emptying
F c. chewing
F d. swallowing
F e. intestinal segmentation.

Q. 118. **Muscle tone in the lower esophagus is**
T a. increased by gastrin
T b. greater than that in the middle esophagus
T c. a major factor in preventing heart-burn
F d. increased in pregnancy
F e. increased by anticholinergic drugs.

Q. 119. **Factors that depolarize the membrane of gastrointestinal smooth muscle are**
T a. stimulation by parasympathetic nerves
T b. stimulation by gastrointestinal tract hormones
F c. shortening of the muscle
F d. inhibition by acetylcholine
F e. stimulation by epinephrine and norepinephrine.

Q. 120. **Factors that can excite the enterogastric reflexes are**
T a. osmolality of the chyme
T b. presence of irritation in duodenal mucosa
F c. contraction of the duodenum
F d. alkalinity of the duodenal chyme
F e. break down products of fats.

Q. 121. **Gastro-colic reflex is related to**
T a. Mass preistalsis
F b. Segmental movement
F c. Pendular movement
F d. Colonic disorder
F e. None.

Q. 122. **The following simulate enterogastric reflex?**
T a. Products of protein digestion in the duodenum
T b. Duodenal distension
T c. H^+ ions bathing duodenal mucosa
F d. Hormones
F e. None.

Q. 123. **Which of the following does not simulate enterogastric reflex?**
F a. Products of protein digestion in the duodenum
F b. Duodenal distension
F c. H^+ ions bathing duodenal mucosa
T d. Hormones.
F e. None.

Q. 124. **Enterogastric reflex is caused by**
T a. Duodenum distension
T b. Increased osmolality of chyme
T c. b and c
F d. Alkaline pH in duodenum
F e. All.

Q. 125. **Enterogastric reflex is caused by**
T a. Duodenum distension
T b. Increased osmolality of chyme
T c. b and c
F d. Alkaline pH in duodenum
F e. All.

Q. 126. **Stimulation for gastric emptying**
T a. Distension.
F b. Secretin
F c. CCK
F d. Gastrin
F e. None.

Q. 127. **Gastric phase of gastric secretion is caused by**
T a. chemical substances
T b. polypeptides
T c. natural substances
T d. hormones
F e. iron.

Q. 128. **Cephalic phase of gastric secretion is mediated by**
T a. Gastrin
F b. Neurohormones
F c. Parasympathetic
F d. Sympathetic
F e. None.

Q. 129. **Cephalic phase of gastric secretion**
T a. starts immediately after food enters the mouth
T b. is mediated by parasympathetic nerve
F c. is not influenced by mucus
F d. leads to 100% of gastric secretions
F e. is mediated by sympathetic nerve.

Q. 130. **Most potent stimulus for secretin is**
T a. Acid chyme
F b. Dilatation of intestine
F c. Protein
F d. Fat
F e. None.

Q. 131. **Gastric emptying is decreased by all except**
- T a. Hypoosmolarity in duodenum
- F b. Fatty meal
- F c. Hyperosmolarity in duodenum
- F d. Distension of duodenum
- F e. None.

Q. 132. **Gastric emptying is decreased by**
- T a. Fatty meal
- T b. Hyperosmolarity in duodenum
- T c. Distension of duodenum
- F d. Hypoosmolarity in duodenum
- F e. None.

Q. 133. **Gastric secretion is**
- T a. Increased by stomach distention
- F b. Inhibited by curare
- F c. Stimulated by nor adrenaline
- F d. Stimulated by an increase in tonic activity
- F e. None.

Q. 134. **The gastric phase of gastric secretion is brought about by**
- T a. Hormonal factors
- F b. Neural factors
- F c. Gastric distension
- F d. Presence of proteins in the stomach
- F e. All.

Q. 135. **Best stimuli for secretin secretion is**
- T a. Acid
- F b. Protein
- F c. Fat
- F d. Bile
- F e. None.

Q. 136. **Best stimuli for CCK secretion is**
- T a. Fat
- F b. Acid
- F c. Protein
- F d. Bile
- F e. None.

Q. 137. **Most potent simulus for bile secretion is**
- T a. Bile salt
- F b. Cholecystokinin
- F c. Gastrin
- F d. Secretin
- F e. Bile acid

Q. 138. **The role of chromium in the body is**
- T a. Facilitates action of insulin
- F b. Erythropoiesis
- F c. Growth and development
- F e. None.
- F d. Spermatogenesis

Movements of GIT

Q. 139. **Antiperistalsis**
- T a. helps in to and fro movement
- T b. causes vomiting.
- T c. serves to mix the chyme with digestive juice
- F d. causes movement of food bolus.
- F e. propels the intestinal contens towards ileocolic sphincter

Q. 140. **As the masticated food passes through the esophagus**
- T a. stomach receives food
- T b. stomach shows receptive relaxation
- F c. cardiac sphincter constricts
- F d. pyloric sphincter relaxes
- F e. duodenum constricts

Q. 141. **Pyloric sphincter**
- T a. regulates passage of chyme from stomach to duodenum
- T b. prevents back flow of chyme from duodenum to stomach
- F c. mixes food with gastric juice
- F d. forces chyme from stomach to duodenum
- F e. prevents digestion of stomach.

Q. 142. **Stomach reflexly**
- T a. stimulates bile expulsion
- T b. stimulates salivation
- T c. increases peristaltic movements in the last part of ileum
- F d. inhibits pancreatic secretion
- F e. decreases peristaltic movements in the colon.

Q. 143. **The passage of gastric contents to the dudenum may cause**
- T a. copious secretion of pancreatic juice rich in bicarbonate
- T b. decreased gastric motility
- T c. contraction of the gall bladder
- F d. contraction of the pyloric sphnicter
- F e. release of gastrin.

Q. 144. **Factors that inhibits stomach emptying include**
- T a. enterogastric reflex
- T b. CCK
- T c. increased acidity of duodenal chyme.
- F d. gastrocolic reflex
- F e. gastrin

Q. 145. **Hormones that inhibits gastric emptying are**
- T a. secretin
- T b. GIP
- T c. CCK

F d. gastrin
F e. motilin

Q. 146. **Gastric emptying is stimulated by**
T a. distention of stomach
T b. increased gastric motility.
F c. distention of duodenum
F d. presence of fatty acids
F e. decreased gastric motility

Q. 147. **Gastric emptying is inhibited by**
T a. decreased gastric motility.
T b. distention of doudenum
F c. presence of protein, alcohol in stomach
F d. increased secretion of gastrin
F e. relaxation of pyloric sphincter

Q. 148. **Gastric emptying is primarilly controlled**
T a. when chyme enters the intestine
F b. during chewing
F c. during swallowing
F d. when chyme enters the stomach
F e. during the interodigestive period.

Q. 149. **Small intestine has**
T a. four types of movement
T b. pendular movement
F c. three types of movement
F d. two types of movement
F e. retropulsive movement.

Q. 150. **Small intestinal motility is enhanced by**
T a. insulin.
T b. gastrin
T c. cholecystokinin
F d. glucagon
F e. secretin

Q. 151. **Small intestinal motility is inhibited by**
T a. secretin
T b. glucagon.
F c. insulin
F d. gastrin
F e. cholecystokinin

Q. 152. **Functions of the colon include**
T a. absorption of water
T b. absorption of electrolytes
T c. storage of fecal matter.
F d. emptying of food
F e. prevention of back flow of fecal matter

Q. 153. **Mechanical movements of the large intestine include**
T a. haustral churning
T b. mass peristalsis.
F c. mixing movement
F d. pendular movement
F e. retropulsive movement

Q. 154. **Peristaltic rush means**
T a. powerful peristalsis
T b. diarrhoea.
F c. mass movement
F d. rapid antiperistalsis
F e. weak peristalsis

Q. 155. **Regarding defecation reflex**
T a. the stretch receptors are in the rectal wall
T b. it is co-ordinated by reflex centres in the spinal cord
T c. it can be voluntarily inhibited
F d. its afferent limb carries impulses from stretch receptors
F e. its efferent limb travels through sympathetic nerve.

Q. 156. **Vomiting**
T a. starts with salivation and the sensation of nausea.
T b. is antiperistalsis
F c. is usually preceded by decreased heart rate
F d. center is present in the thalamus
F e. begins with a deep expiration.

Q. 157. **Adynamic ileus**
T a. may occur after abdominal operation.
T b. occurs when the intestine are traumatized
T c. can be relieved by aspirating the fluid and gas
F d. is a direct stimulation of smooth muscle
F e. causes increased intestinal motility

Applied

Q. 158. **Cholelithiasis**
T e. occurs due to bile stasis.
T b. incidence increases with age
T c. occurs in 20% of the woman and in 5% of the men
F a. is the absence of gall stones
F d. occurs between the ages of 20-30 years

Q. 159. **Gastroesophageal reflux disease**
T a. is caused by lower esophageal sphincter incompetence
T b. permits reflux of acid
T c. is due to regurgitation of food
T d. causes heart-burn
F e. is same as achalasia

Q. 160. **Hemorrhoids**
T a. are caused by improper bowel habit.
T b. develop when the veins are engorged with blood
T c. may be caused by constipation
F d. are saclike outpouching of the wall of the colon
F e. cause an inflammation within the diverticula

Q. 161. **Constipation**

T a. is caused by improper bowel habits.
T b. refers to infrequent or difficult defecation
F c. increased motility of the intestines
F d. is decreased water absorption
F e. is caused by lactose intolarance

Q. 162. **Causes of alkalosis are**

T a. complete water deprivation for 24 hours.
T b. severe persistent vomiting
T c. excessive sweating
F d. severe diarrhea
F e. drinking of sodium lactate solution

Q. 163. **Cause of acidosis is**

T a. severe diarrhoea
F b. severe persistent vomiting
F c. excessive sweating
F d. drinking of sodium lacate solution
F e. complete water deprivation for 24 hours.

Q. 164. **Total gastrectomy causes**

T a. malabsorption of protein
T b. impaired fat absorption
T c. vitamin B_{12} malabsorption
F d. haemodilution after meals
F e. grossly reduced iron absorption

Q. 165. **Surgical removal of about 90% of the ileum and jejunum tends to cause**

T a. An increase in fat content of stool
T b. Demineraiisation of bones
T c. Anaemia.
F d. A fall in extracellular fluid volume
F e. None.

11
Food & Nutrition

Food

a. ***Definition*** : Any material that provides the nutritive requirements of an organism to maintain growth and well being.

or *(Ref. Taber's)*

Foods are those chemical substances which an individual takes, digests, assimilates and provides the nutritive requirements of an individual to maintain growth and physical well being.

b. ***Fuctions of food*** :

1. It supply energy for production of heat and for all types of activities.
2. Essential for growth of human body,
3. Essential for the repair of the daily wear & tear.
4. Protects the body from various types of diseases.
5. In a general way, it is involved in the functioning of the body processes.

c. ***Main constituents or proximate principles of food*** :

i. Proteins
ii. Fats
iii. Carbohydrates
iv. Vitamins
v. Minerals (salt) and
vi. Water.

d. ***Calorie value of food*** :

Energy in each gm of the three different food stuffs in diet is :

	Calories
Carbohydrate	4.4
Fat	9.0
Protein	4.0

(Ref. Guyton & Hall-11th edition; page 865)

e. ***Metabolic end product of food*** :

Carbohydrate	:	Energy + CO_2+ H_2O
Fat	:	Energy + CO_2+ H_2O
Protein	:	Energy + Urea, Uric acid, Creatinine

f. ***Percentage of different food in a balance diet*** :

Carbohydrate	:	60-70% of total diet
Fat	:	20-25% of total diet
Protein	:	15% of total diet.

Classification of food

a. *According to the sources of origin :*
   i. Animal foods : Milk, egg, meat etc.
   ii. Plant foods : Vegetables, cereals, pulses etc.

b. *According to the calorigenicity :*
   i. Calorigenic foods : The foods which give calorie that is necessary for energy production, growth and maintenance of tissues, e.g carbohydrate, protein and fat.
   ii. Non-calorigenic foods : The foods which do not provide any calorie but necessary for chemical mechanisms i.e. for utilization of energy, for synthesis of various metabolites, hormones and enzymes. These are vitamins, minerals and water.

c. *According to their main functions :*
   i. Fuel or energy yielding foods : Thses foods are rich in carbohydrates and fats, e.g cereals, sugar, roots, tuber etc.
   ii. Body Building foods : These foods are rich in proteins. e.g. Meat, liver, fish, milk, pulses.
   iii. Protective foods : These foods are rich in proteins, vitamins and minerals, e.g milk, egg, liver, green vegetables and fruits.

Nutrition

Definition : Nutrition is a dynamic process concerning with ingestion, digestion, absorption, and assimilation (metabolism) of food substances by which growth, repair and maintenance of activities in the body as well as a whole or in any of its parts are accomplished.

(Ref. Taber's)

Aim of nutrition :

1. To meet up the calorie demand of the individual.
2. To meet up specific requirements of individual item of food stuff.
3. To formulate and plan a diet.

Criteria of good nutrition :

i. It should protect the body from infection and deficiency diseases.
ii. It should nourish the body and make the person energetic.
iii. It should help in making a fair complexion of the body and protect it from obesity.

Sign of good nutrition :

i. Smooth and shiny skin
ii. Glossy hair
iii. Well developed muscles, bones and teeth
iv. The subject appears to be of strong build and energetic.

Nutrient : Nutrient means chemical ingredients present in food which produce energy. In other words, any substance nourishing the body.

Malnutrition : It may be defined as a pathological state resulting from a relative or absolute deficiency or excess of one or more essential nutrients. Here calorie requirement is adequate but proportion of proximate principles of food is not adequate. That is "Adequate but not proportionate."

Subnutrition : It is a condition which results when insufficient food is eaten over an extended period of time. Here calorie requirement is not adequate but proportion of proximate principles of food is normal. That is "proportionate but not adequate".

Diet

Diet is the designed calculated amount of food for an individual for a particular condition of body. An adequate diet is one which permits-

i. Normal health
ii. Maintenance and
iii. Reproduction.

A normal diet should consists of all the proximate principles of food.

Essential dietary components : An optimal diet includes, in addition to suffucient water, adequate calories, protein, fat, minerals and vitamins.

(Ref. Ganong 22th Edition; Page 311)

Balanced Diet

a. *Definition* : Balanced diet is a diet containing all the proximate principles of food in adequate and proportionate amount; including essential aminoacids and fatty acids for normal growth, activity, reproduction and lactation.

b. *Adequate :* Means the amount that supply the exact calorie.

c. *Proportionate amount :* Means presence of appropriate proportion of different food stuffs.

Carbohydrate : Protein : Fat = 4 : 1 : 1

d. ***Factors considered to formulate a balanced diet*** :

i. Age
ii. Sex
iii. Quality and quantity of food
iv. Socioeconomical values
v. Seasonal factor
vi. Geographical factor
vii. Allergic condition.

e. ***Criteria of a balanced diet*** :

i. It should contain all the proximate principles of food in adequate and proportionate amount.
ii. One third to half of protein and fat should come from animal sources.
iii. It should contain sufficient fruits and vegetables.
iv. It should be easily digestable, absorbable and assimilable.
v. It should be easily available.
vi. It should contain certain amount of cellulose to promote peristalsis.

Calories

i. *Definition* : The standard unit of heat energy is the **calorie (cal)**, defined as the amount of heat energy necessary to raise the temperature of 1 gm of water 1 degree from 15°c to 16°c.

ii. Unit : The unit is also called the gram calorie, small calorie, or standard calorie.

The unit commonly used in physiology, and medicine is the **Calorie (kilocalorie: kcal)**, which equals 1000 cal.

(Ref. Ganong 22th Edition; Page 280)

Approximate calorie requirment :

Group	*Particulars*	*Calorie require*
Adult male (55 kg)	Sedentary worker	2400 kcal/day
	Moderate worker	2800 kcal/day
	Heavy worker	3900 kcal/day
Adult female (45 kg)	Sedentary worker	1900 kcal/day
	Moderate worker	2200 kcal/day
	Heavy worker	3000 kcal/day
Pregnant mother	Additional allowance	+ 300 kcal/day
Lactating mother	Additional allowance	+ 550 kcal/day
Infants	0—6 months	120 kcal/day
	7—12 months	100 kcal/day
Children	1—3 years	1200 kcal/day
	4—6 years	1500 kcal/day
	7—9 years	1800 kcal/day
	10—12 years	2100 kcal/day

Adeloscents	13—15 years - Boys	2500 kcal/day
	Girls	2200 kcal/day
	16—18 years - Boys	3000 kcal/day
	Girls	2200 kcal/day

(Ref. JE park and K Park 11th and others)

Nutrition and food science institute, Dhaka University has recommended the daily calorie requirement as follows :

1. Male (55 kg) : 2400 kcal/day
2. Female (45kg) : 1900 kcal/day
3. Pregnant mother : 2100 kcal/day
4. Lactating mother : 2300 kcal/day

N.B. 25 to 50% of which should come from protein.

Daily calorie requirements depend upon :

i. Basal metabolic rate.
ii. Nature of work to be done.
iii. Specific dynamic action (S.D.A).

Caloric intake and distribution

Dietary intake : The calotic value of the dietary intake must be approximately equal to the energy expended if body weight is to be maintained. In addition to the 2000 kcal/d necessary to meet basal needs, 500-2500 kcal/d (or more) are required to meet the energy demands of daily activities.

Distribution of the calories : The distribution of the calories among carbohydrate, protein, and fat is determined partly by physiologic factors and partly by taste and economic considerations.

Protein : A daily protein intake of 1 g/kg body weight to supply the eight nutritionally essential amino acids and other amino acids is desirable. The source of the protein is also important. ***Grade I proteins***, the animal proteins of meat, fish, dairy products, and eggs, contain amino acids in approximately the proportions required for protein synthesis and other uses. Some of the plant proteins are also grade I, but most are ***grade II*** because they supply different proportions of amino acid and some lack one or more of the essential amino acids. Protein needs can be met with a mixture of grade II proteins, but the intake must be large because of the amino acid wastage.

Fat is the most compact form of food, since it supplies 9.3 kcal/gm. However, often it is also the most expensive. Indeed, internationally there is a reasonably good positive correlation between fat intake and standard of living. In the past, Western diets have contained large amounts (100 g/d or more). The evidence indicating that a high unsaturated/saturated fat ratio in the diet is of value in the prevention of atherosclerosis and the current interest in preventing obesity may change this. In Central and South American Indian communities where corn (carbohydrate) is the dietary staple, adults live without ill effects for years on a very low fat intake. Therefore, provided that the needs for essential fatty acids are met, a low-fat intake does not seem to be harmful, and a diet low in saturated fats is desirable.

Carbohydrate is the cheapest source of calories and provides 50% or more of the calories in most diets.

In the average middle-class American diet, approximately 50% of the calories come from carbohydrate, 15% from protein, and 35% from fat.

When calculating dietary needs, it is usual to meet the protein requirement first and then split the remaining calories between fat and carbohydrate, depending on taste, income, and other factors.

For example, a 65-kg man who is moderately active needs :

i. About 2800 kcal/d.
ii. He should eat at least 65 g of protein daily, supplying 267 (65 x 4.1) kcal. Some of this should be grade I protein.
iii. A reasonable figure for fat intake is 50-60g.
iv. The rest of the caloric requirement can be met by supplying carbohydrate.

(Ref. Ganong 22th Edition; page 311)

Mineral & vitamin reqirements

Alredy discussed in chapter 3 and 4

Diet of growing children

1. *Energy requirment :* With advance in age, there is increase in calore requirements of the child due to more physical activities on their part.

   The energy requirments of a child aged 1 year is about 1,000 kcal/day.

   After the age of 1 year, the energy needs can be computed by adding 100 kcal for every year of life.

   Thus a child of 5 years needs - 1500 Kcal/day.

2. *Proteins* : Extra proteins are needed to ensure proper growth of their tissues. 8 to 10 % of the energy need may be given as proteins.
3. *Calcium and phosphorus* : Adeuqate amount are needed for the growth of bones and teeth.
4. *Iron :* Adequate amount for haemoglobin.
5. *Vtamins :* Adequate amount.

Q. ***What is the minimum carbohydrate requirement to prevent ketosis?***

Ans. A minimum of 5 gm of carbohydrate for 100 calorie of total diet is necessary to prevent the development of ketosis.

Protein, fat, and carbohydrate content of different foods

Food	*% Proteins*	*% Fat*	*% carbohy drate*	*Fuel value per 100 Grams Calories*
Apples	0.3	0.4	14.9	64
Asparagus	2.2	0.2	3.9	26
Bacon, fat	6.2	76.0	0.7	712
broiled	25.0	55.0	1.0	599
Beef, medium	17.5	22.0	1.0	268
Beets, fresh	1.6	0.1	9.6	46
Bread, white	9.0	3.6	49.8	268
Butter	0.6	81.0	0.4	733
Cabbage	1.4	0.2	5.3	29
Carrots	1.2	0.3	9.3	45
Cashew nuts	19.5	47.2	26.4	609
Cheese Cheddar, American	23.9	32.3	1.7	393
Chicken, total edible	21.6	2.7	1.0	111
Chocolate	(5.5)	52.9	18.0	570
Corn (maize) entire	10.0	4.3	73.4	372
Haddock	17.2	0.3	0.5	72
Lamb, leg, interrnediate	18.0	17.5	1.0	230
Milk, fresh whole	3.5	3.9	4.9	69
Molasses medium	0.0	0.0	(60.0)	240
Oatmeal, dry, uncooked	14.2	7.4	68.2	396
Oranges	0.9	0.2	11.2	50
Peanuts	26.9	44.2	23.6	600
Peas, fresh	6.7	0.4	17.7	101
'Pork, ham, medium	15.2	31.0	1.0	340
Potatoes	2.0	0.1	19.1	85
Spinach	2.3	0.3	3.2	25
Strawberries	0.8	0.6	8.1	41
Tomatoes	1.0	0.3	4.0	23
Tuna, canned	24.2	10.8	0.5	194
Walnuts, English	15.0	64.0	15.6	702

(Ref. Guyton & Hall-11th edition; Page 866)

Chart of Energy expenditure of male

A. 8 hours in bed at BMR = 35.5 x 1.62 x 8 = 460 kcal

B. 8 hours non-occupational work : = 1220 kcal

1. 1 hour personal necessities such as dressing, undressing, washing, shaving, bathing etc at 3.0 kcal/kg/hour. = 165 kcal
2. 2 hour walking at 4.0 kcal/kg/hr = 440 kcal
3. 4 hour sitting & standing activites at 1.7 kcal/kg/hr = 374 kcal
4. 1 hour recreation at 4.4 kcal/kg/hr = 241 kcal

Total = 1220 kcal

C_1. 8 hours sedentary occupation overall rate 1.7 kcal/kg/hr. ***or*** = 750 kcal

C_2. 8 hour moderate industrial work overall rate 2.5 kcal/kg./hr. ***or*** = 1000 kcal

C_3. 8 hours heavy work overall rate 5 kcal/kg./hr. = 2200 kcal

Total net calories for :

i. Light or sedentary work = A + B + C_1 = 2430 kcal

ii. Moderate work (Industrial) = A + B + C_2 = 2780 kcal

iii. Heavy work = A + B + C_3 = 3880 kcal

Chart of energy expenditure of female

A. 8 hours in bed at BMR = 31.6x1.4 x 8 = 354 kcal

B. 8 hours non-occupational work = 826 kcal

C_1. 8 hours sedentary-occupational work at 1.7 kcal/kg/hr = 610 kcal

C_2. 8 hours moderate work overall rate at 2.5 kcal/kg/hr = 900 kcal

C_3. 8 hours heavy occupational work at 5 kcal/kg./hr. = 1800 kcal

Total net calories for :

i. Sedentary work : A + B + C_1 = 1790 kcal

ii. Moderate work : A + B + C_2 = 2080 kcal

iii. Heavy work : A + B + C_3 = 2980 kcal

Balanced diet chart

1. ***Sedentary worker*** :

Protein	55 gm	220 kcal
Fat	55 gm	495 kcal
Carbohydrate	400 gm	1600 kcal
Green leafy vegetables	100 gm	25 kcal
Fruits	30 gm	15 kcal
Other vegetables	75 gm	45 kcal
	Total =	2400 kcal

SDA of food 200 kcal.

So, total = 2400 + 200 kcal
= 2600 kcal.

2. ***Heavy worker*** :

Protein	55	gm	220 kcal
Fat	70	gm	630 kcal
Carbohydrate	650	gm	2600 kcal
Green vegetables	125	gm	30 kcal
Other vegetables	150	gm	90 kcal
Fruits	60	gm	30 kcal
			= 3600 kcal

SDA of food = 200 kcal.

So, total = 3600 + 200 kcal
= 3800 kcal.

3. ***Adult woman*** :

Protein	45	gm	180 kcal
Fat	45	gm	405 kcal
Carbohydrate	300	gm	1200 kcal
Green vegetables	100	gm	25 kcal
Other vegetables	75	gm	45 kcal
Fruits	30	gm	15 kcal
			= 1870 kcal

200 Kcal should be added to allow to SDA of food.

So, total = 1870 + 200 kcal
= 2070 kcal

4. ***Pregnant mother*** :

Protein	(45 + 30)	gm	300 kcal
Fat	45	gm	405 kcal
Carbohydrate	350	gm	1400 kcal
Green leafy vegetables	125	gm	30 kcal
Other vegetables	100	gm	60 kcal
Fruits	30	gm	15 kcal
			= 2210 kcal

200 kcal should be added to allow for SDAof food.

So, total = 2210 + 200
= 2410 kcal.

Nutritional deficiency disease

According to WHO expert committee nutritional deficiency diseases are classified as :

A. *Protein-energy malnutrition :*
   i. Kawashiorkor
   ii. Marasmus
   iii. Marasmic Kawashiorkor

B. *Avitaminosis :* Deficiency of vitamins -
   i. Vitamin A deficiency
   ii. Thiamine & Niacin deficiency states
   iii. Deficiency of B. complex components.
   iv. Ascorbic acid deficiency
   v. Vitamin D deficiency

C. *Obesity & other hypervitaminosis :*
   i. Obesity
   ii. Hypervitaminosis A.
   iii. Hypercarotinaemia.
   iv. Hypervitaminosis D.

   N.B. Fe deficiency
   Iodine defiency.

Difference between Kawashiorkor & Marasmus

Features	*Marasmus*	*kawashiorkor*
1. Cause	Due to deficiency of calorie	Due to deficiency of protein.
2. Oedema	Absent	Present in lower legs.
3. Muscle wasting	Severe	Sometimes
4. Growth retardation	Severe	Less than marasmus
5. Appetite	Usually good	Usually Poor
6. Skin change	Usually none	Often diffuse depigmentation
7. Moon face	None	Often.

Marasmus

i. Cause : Due to deficiency of calorie

ii. *Characteristic features of marasmus :*
   a. Muscle wasting : Severe
   b. Growth retardation : Severe
   c. Appetite : Usually good
   d. Skin change : Usually none
   e. Oedema : Absent

Kawashiorkor

i. Cause : Due to deficiency of protein.

ii. *Characteristic features of kawashiorkor :*

a. Oedema	:	Present in lower legs
b. Moon face	:	Often.
c. Muscle wasting	:	Sometimes
d. Growth retardation	:	Less
e. Appetite	:	Usually poor
f. Skin change	:	Often diffuse pigmentation

Phrenoderma

It is a nutritional deficiency disease of skin, results from dietary deficiency of essential fatty acids characterized by horny papular eruptions on the posterior and lateral aspects of the limbs and on the back and buttocks.

It can be cured by the administration of lineseed or sufflower seed oil along with vitamin B-complex.

Neurolathyrism

a. *Definition :* It is a disease of the nervous system characterized by gradually developing paralysis of the lower limbs, caused by Lathyrus sativus.

b. *Cuase* : Diet containing 30-40% Lathyrus sativus (Khesarihdal) for 2 to 6 months will cause the disease. The causative factors is some neurotoxins -

i. Beta-oxalyl amino alanine (BOAA)

ii. Alpha-Beta isomer of mono-oxalyl di-aminopropionic acid.

c. *Clinical stages* : Clinically the disease has 5 stages-

i. Latent stage
ii. No-stick stage
iii. One-stick stage
iv. Two-stick stage
v. Crowler stage.

d. *Prevention :*

i. Banning the crop/Avoiding khesaridal in diet
ii. Removal of toxins from food
iii. Geuetic approach.

(Ref. Community medicine; J.E. Park - 12th - 344)

Colostrum

a. *Definition :* Colostrum is the secretion of breast following child birth for the first 2-3 days which contains a great quantity of proteins and calories.

b. *Contents :*

i. Protenin (Moderate)
ii. Sugar (Few)
iii. Minerals (high)
iv. Antibody specially secretory IgA (high)
v. Fat.

c. *Importance :*

i. Antibodies (IgA) play an important role in protection against infection.
ii. It may help to sterilize the small intestine.
iii. It possesses laxative quality.

Weaning

It is the process starting around the age of 5 to 6 months in which an infant's diet pattern is gradually changed from breast milk to supplementary food.

Weaning should start after 6 months. Breast milk alone can not sustain the growth of the infant. Supplementary foods are- soft cooked rice, washed potatoes, soft cooked vegetables, dhal water, fruit juice, egg etc.

Q. **Why milk is an ideal food?**

Ans. Milk is an ideal food because -

1. Milk is unique in nutritive value and contains all the food factors of a well balanced diet required for human body.
2. It is easily digestable, absorbable and assimilable.
3. Human milk is in sterile form in lower temperature.
4. Skimmed milk powder is devoid of fat & fat soluble vitamins but a good source of protein, calcium and water soluble vitamins.

Milk Injury

Definition : It is a condition where a child becomes flabby, apathetic dull, anaemic and susceptable to all sort of diseases due to consumption of milk only over a long period like 1 to 1.5 year without taking any other food.

Cause : Milk contains less iron & vitamin C. So, continuous consumption of milk after 6 months develops first iron deficiency anaemia and then scurvy. The childs also becomes flabby, edematous due to ingestion of more water in milk.

Prevention : It can be prevented by weaning or supplementary food.

(Ref. Community medicine; J.E. Park)

Humanisation of Cow's Milk

Cow's milk is to be suitably changed to make it comparable to mothers milk and to make a substitute drink for young baby, even a new one.

Principle : The insoluble caseinogen of cow's milk must be reduced to the level as present in human milk, the amount of lactose must be increased to the right proportion and the resulting mixture must be pasteurised.

Procedure : This is done by adding 1 part of water to 1 part of cow's milk, this will bring down the proten content to that of mother's milk, but the sugar & fat content also come down. So, 1 oz of milk sugar and 1 oz of ordinary

centrifused cream should be added to 1 pint of diluted milk. Vit-C should be given from second month on ward.

Pasteurization

i. *Defination* : According to WHO heating of milk to such temperature and for such periods of time as are required to destroy any pathogens that may be present while causing minimal changes in the composition, flavoure and nutritive value.

ii. *Methods* : There are 3 widely used mehtods-

1. *Holder mehtod* : In this method, milk is kept at 63-66°C for at least 30 minutes and then quickly cooled to 5°C.
2. *Flash method or High temperature and short time method* : Milk is rapidly heated to a temperature of nearly 72 C for less than 15 second and is then rapidly cooled to 4°C.
3. *Ultra-High temperature method :* Milk is rapidly heated usually in two stages (the second stage usually being under pressure) to between 125°C for a few second only. It is then rapidly cooled and bottled as quickly as possible.

iii. *Tests of pasteurized milk* :

1. *Phosphatase test* : Phosphatase, an enzyme useally present in milk and inactivated during pasteurization. Its presence in milk indicates inadequate pasteurization.
2. Standard plate count.
3. Coliform count.

Calorie value of an egg

An egg weighting 60 gm, supplies 6 gm protein, 6 gm fat, about 30 mg carbohydrate, 1.5 mg iron and rich in all the vitamins except vit -C.

Total calorie value = (24 + 54)
= 78 kcal.

Basal Metabolic Rate (BMR)

i. *Definition :* The metabolic rate at basal condition of the body is called basal metabolic rate.

(Ref. Guyton & Hall-11th edition)

ii. *The basal conditions are :*

a. The patient should be awake.
b. The patient should be completely both mental and physical rest.
c. The patient should remain in normal condition of environment- normal temperature, pressure and humidity (20-25°C)
d. The person should be without food at least for about 12-18 hours. (post-absorptive state).

(Ref. Guyton & Hall-11th edition)

iii. *Normal value* :

a. In male : 40 cal/sq.m of body surface area/hour.
b. In female : 37 cal/sq.m of body surface area /hour.

v. ***Factors affecting the metabolic rate.***

a. Muscular exertion during or just before measurement
b. Recent ingestion of food
c. High or low environmental temperature
d. Height, weight, and surface area
e. Sex
f. Age
g. Growth
h. Reproduction
i. Lactation
j. Emotional state
k. Body temperature
l. Circulating levels of thyroid hormones
m. Circulating epinephrine and norepinephrine levels

(Ref. Ganong 22th Edition; Page 281)

vi. ***B M R increased in*** :

i. Hyperthyroidism
ii. Leukemia
iii. Polycythemia
iv. Cardiac failure
v. Hypertension
vi. Fever.

vii. ***BM.R decreased in*** :

i. Hypothyroidism
ii. Starvation
iii. Addison's disease
iv. Lipid nephrosis
v. Prolonged malnutrition.

viii. ***Importance of BMR*** :

i. For prescribing a diet of adequate calorie value
ii. For the diagnosis of various pathological condition such as hyperthyroidism, hypothyroidism
iii. To note the effect of different types of food & drug on BMR.

Metabolic rate

a. *Definition :* The amount of energy liberated per unit of timc is the *metabolic rate.*

(Ref. Ganong 22th EDition; Page 279)

b. *Measurement :* Metabolic rate is measured in two ways -
i. Direct calorimetry
ii. Indirect calorimetry.

Direct calorimetry : In this way, metabolic rate is determined by measuring the quantity of heat liberated from the body in

a large specially constructed calorimeter.

Indirect calorimetry : Measurement of BMR in man is conveniently done by indirect calorimetry, using the Benedict-Roth recording spirometer. From the spirometer we have to determine the volume of oxygen consumption and carbondi- oxide expiration. The RQ is assumed to be 0.83 (non-protein RQ on mixed diets). BMR is then calculated from the heat produced by the volume of oxygen consumed, depending on the caloric equivalent of 1 liter O_2 at RQ - 0.83.

Both CO_2 output and O_2 consumed can be directly measured without the need to assume the RQ, if Knipping's spirometer is used.

(Ref. Biochemistry-Debajyote Das)

Respiratory Quotient (RQ)

i. *Definition :* It is the ratio of the volume of CO_2 produced by the volume of O_2 consumed.

RQ = (Volume of CO_2 produced / Volume of O_2 consumed)

ii. *Factors affecting RQ* :

1. *Role of diet :*
   a. Carbohydrate : In case of carbohydrate RQ is unity or 1. Because the volume of CO_2 produced is same as the volume of O_2 consumed.
   b. Fat : In case of fat, respiratory quotient is 0.7.
   c. Protein : In case of protein RQ is 0.8.
   d. For mixed diet : RQ is 0.85.
2. *Acidosis :* RQ is higher or increases, because CO_2 production is more than O_2 consumption.
3. Alkalosis : RQ falls, because respiration is depressed & CO_2 will retain in the body.
4. Temperature : Increase temperature increases RQ.
5. Diabetes mellitus .
6. Prolong starvation .
7. Voluntary hyperpnoea.

Energy balance, metabolism and nutrition

The endocrine system, like the nervous system, adjusts and correlates the activities of the various body systems, making them appropriate to the changing demands of the external and internal environment. Endocrine integration is brought about by chemical signals secreted by ductless glands and transported in the circulation to target cells. Some of the hormones are amines, and others are amino acids, polypeptides, proteins, or steroids.

Metabolism : The hormones regulate metabolic processes. The term *metabolism*, literally meaning "change," is used to refer to all the chemical and energy transformations that occur in the body.

The animal organism oxidizes carbohydrates, proteins, and fats, producing principally CO_2, H_2O, and the energy necessary for life processes. CO_2, H_2O, and energy are also produced when food is burned outside the body.

Catabolism : However, in the body, oxidation is not a onestep, semiexplosive reaction but a complex, slow, stepwise process called *catabolism*, which liberates energy in small, usable amounts.

Aanbolism : Energy can be stored in the body in the form of special energy-rich phosphate compounds and in the form of proteins, fats, and complex carbohydrates synthesized from simpler molecules. Formation of these substances by processes that take up rather than liberate energy is called *anabolism*.

Metabolic rate : The amount of energy liberated per unit of timc is the *metabolic rate.*

(Ref. Ganong 22th EDition; Page 279)

Energy intake and output are balanced under steady-state conditions : Intake of carbohydrates, fats, and proteins provides energy that can be used to perform various body functions or stored for later use. Stability of body weight and composition over long periods requires that a person's energy intake and energy expenditure be balanced.

When a person is *overfed* and energy intake persistently exceeds expenditure, most of the excess energy is stored as fat, body weight increases; conversely, *loss of body mass* and *starvation* occur when energy intake is insufficient to meet the body's metabolic needs.

Because different foods contain different proportions of proteins, carbohydrates, minerals, and vitamins, appropriate balances must also be maintained among these constituents so that all segments of the body's metabolic systems can be supplied with the requisite materials.

(Ref. Guyton & Hall-11th Edition; Page 865)

Average daily requirement for protein is 30 to 50 grams : 20 to 30 grams of the body proteins are degraded and used to produce other body chemicals daily. Therefore all cells must continue to form new proteins to take the place of those that are being destroyed, and a supply of protein is needed in the diet for this purpose. An average person can maintain normal stores of protein, provide the daily intake is above 30 to 50 grams.

Therefore, individuals in economically disadvantaged countries who consume *cornmeal* as the principal source of protein sometimes develop the protein-deficiency syndrome called ***kwashiorkor*** which consists of failure to grow, lethargy, depressed mentality, and edema caused by low plasma protein concentration.

(Guyton & Hall-11th Edition; Page 866)

Carbohydrates and fats act as Protein Sparers : When the diet contains an abundance of carbohydrates and fats almost all the body's energy is derived from these two substances, and little is derived from proteins. Therefore, both carbohydrates and fats are said to be protein sparers. Conversely, in starvation, after the carbohydrates and fats have been depleted. the body's protein stores are consumed rapidly for energy, sometimes at rates approaching several hundred grams per day rather than the normal daily rate of 30 to 50 grams.

(Guyton & Hall-11th Edition; Page 866)

Regulation of food intake and energy storage

Only about 27 per cent of the *energy ingested normally reaches* the functional systems of the cells, and much of this is eventually converted to heat, which is generated as a result of protein metabolism, muscle activity, and activites of the various organs and tissues of the body. Excess energy intake is *stored* mainly as fat, where as a deficit energy expenditure eventually equals energy intake or death occurs.

In athlets and laborers, energy expenditure for the high level of muscle activity may be as high as 6000 to 7000 Calories per day, compared with only about 2000 Calories per day for sedetary individuals.

(Guyton & Hall-11th Edition; Page 867)

Neural centers regulate food intake

The sensation of hunger is associated with a craving for food and several other several physiologic effects, such as rhythmical contractions of the stomach and restlessness, which cause the person to search for an adequate food supply. A person's *appetite* is a desire for food, often of a particular type and is useful in helping to choose the quality of the food to be eaten. If the quest for food is successful, the feeling of ***satiety*** occurs. Each of these feelings is influenced by environmental and cultural factors, as well as by physiologic controls that influence specific centers of the brain, especially the hypothalamus.

(Guyton & Hall-11th Edition; Page 867)

The hypothalamus contains hunger and satiety centers : Several neuronal centers of the hypothalamus participate in the control of food intake. The *lateral nuclei of the hypothalamus* serve as a feeding center, and stimulation of this area causes an animal to eat voraciously *(hyperphagia)*. Conversely, destruction of the lateral hypothalamus causes lack of desire for food and progressive *inanition*, a condition characterized by marked weight loss, muscle weakness, and decreased metabolism. The lateral hypothalamic feeding center operates by exciting the motor drives to search for food.

The *ventromedial nuclei of the hypothalamous* serve as the ***satiety center***. This center is believed to give a sense of nutritional satisfaction that inhibits the feeding center. Electrical stimulation of this region can cause complete satiety, and even in the presence of highly appetizing food, the animal refuses to eat *(aphagia)*. Conversely, destruction of the ventromedial nuclei causes voracious and continued eating until the animal becomes extremely obese, sometimes as large as four times normal.

Paraventricular; *dorsomedial*, and *arcuate nuclei* of the hypothalamus also play a major role in regulating food intake. For example, lesions of the paraventricular nuclei often cause excessive eating, whereas lesion of the dorsomedial nuclei usually depress eating behavior. The arcuate nuclei are the sites in the hypothalamus where multiple hormones released from the gastrointestinal tract and adipose tissue converge to regulate food intake as well as enerrgy expenditure.

Neurons and neurotransmitters in the hypothalamus that stimulate or inhibit feeding : There are two distinct types of neurons in the *arcuate nuclei* of the hypothalamus that are especially important as controllers of both appetite and energy expenditure

i. Pro-opimelanocortin (P0MC) neurons that produce α-melanocyte-stimulating hormone (α-MSH) together with cocaine and amphetamine-related transcript (CA RT).
   Function : Activation of the POMC neurons decreases food intake and increases energy expenditure.
ii. Neurons that produce the orexigenic substances neuropeptide Y (NPY) and *agouti-related protein (AGRP)*.

Function : Activation of the NPY-AGRP neurons increases food intake and reduces energy expenditure.

(Guyton & Hall-11th Edition; Page 867)

Neurotransmenters and hormones that influence feeding and satiety centers in the hypothalamus

a. ***Decrease feeding (Anorexigenic)*** :
   i. a-Melanocyte-stimulating hormone (a-MSH)
   ii. Leptin
   iii. Serotonin
   iv. Norepinephrine
   v. Corticotropin-releasing hormone
   vi. Insulin
   vii. Cholecystokinin (CCK)
   viii. Glucagon-like peptide (GLP)
   ix. Cocaine- and amphetamine-regulated transcript (CART)
   x. Peptide YY.

(Guyton & Hall-11th Edition; Page 869)

b. ***Increase feeding (Orexigenic)*** :
   i. Neuropeptide Y (NPY)
   ii. Agouti-related protein (AGRP)

iii. Melanin-concentrating hormone
iv. Orexins A and B
v. Endorphins
vi. Galanin (GAL)
vii. Amino acids (glutamate and g-aminobutyric acid)
viii. Cortisol
ix. Ghrelin.

(Guyton & Hall-11th Edition; Page 869)

Factors that regulate quantity of food intake

Regulation of the quantity of food intake can be divided into :

i. Short-term regulation
ii. Intermediate-term regulation
iii. Short-term regulation.

Short-term regulation : which is concerned primarily with preventing overeating at each meal.

The following are several types of rapid feedback signals that are important for these purposes :

a. Gastrointestinal filling inhibits feeding
b. Gastrointestinal hormonal factors that supress feeding :
   i. Cholecystokinin : Is releasd mainly in response to fat entering the duodenum.
   ii. Peptide YY (PYY)
   iii. Glucagon-like peptide : Presence of food in the intestine enhances *glucagon-like peptide*, which in turn enhances glucose-depended *insulin* production and secretion from the pancreas. PPY and insulin both tend to suppress appetite.
c. Ghrelin- a gastrointestinal hormone- increases feeding.
d. Oral receptors meter food intake.

Intermediate and long-term regulation : which is concerned primarily with maintenance of normal quantities of energy store in the body.

i. *Effects of blood concentration of glucose, amino acids and lipids on hunger and feeding* :
   a. Glucostatic theory of hunger and feeding regulation.
   b. Amniostatic theory of hunger and feeding regulation.
   c. Lipostatic theory of hunger and feeding regulation.

   A decrease in blood glucose, amino acid and or breakdown products of lipids such as the keto acids and some fatty acids, the desire for feeding is increased, eventually returning the blood metabolic concentrations back toward normal.

ii. *Temperature regulation and food intake* : When an animal is exposed to cold, it tends tto increase feeding and when it is exposed to heat, it tends to decrease its caloric intake. This is caused by interaction within the hypothalamus between the temperature-regulatting system and the food intake-regulating system.

   This is important, because increased food intake in a cold animal-
   a. Increase its metabolic rate
   b. Provides increased fat for insulation.

   Both of which tend to correct the cold state.

iii. *Feedback signals from adipose tissue regulate food intake* : When the amount of adipose tissue increases , the adipocytes produce increased amount of leptin. Stimulation of leptin receptor in the hypothalamic nuclei initiates multiple actions that decrease fat storage.

(Ref. Guyton & Hall-11 Edition; Page 870, 871)

12
Body Fluid

Body Water

Amount of wtaer present in the body is called body water. It is 40 litres in a man of 70kg, averaging 57% of total body wt in adult male and 51% in an adult female and it may be as high as 75% of the total body wt.

Role of body water *(Funetion)*

1. It is an essential constituent of all cells of the body and the milieu interior (ECF).
2. It serves as a transport medium by which nutrient pass into cells and excretory products come out.
3. Most of the cellular reactions occur in the body in this fluid medium.
4. It is a valuable solvent in which various substances such as electrolytes, nonelectrolytes, enzymes, hormones, vitamins, even fat soluble compounds are carried from one place to another.
5. It plays a vital role in maintenance of body heat.
6. It is helpful in maintaining the form and texture of the tissue.

Daily intake of body water (in ml/day)

	Normal	*Prolonged heavy exercise*
Fluids ingested	2100	?
From metabolism (oxidation of carbohydrate)	200	200
Total intake	*2300*	*?*

(Ref. Guyton & Hall-11th Edition, Page-292)

Daily loss (output) of body water (in ml/day)

	Normal	*Prolonged heavy exercise*
Insensible - Skin	350	350
Insensible - Lungs	350	650
Sweat	100	*5000*
Feces	100	100
Urine	1400	*500*
Total output	*2300*	*6600*

(*N.B. Insensible water loss :* We are not conciously aware of it, even though it occurs in all living humans.)

(Ref. Guyton & Hall-11th Edition, Page-292)

Water balance

The balance between water intake and water output of the body is called water balance.

Classification of water balance

Water balance are of two types :

a. Positive water balance
b. Negative water balance.

Positive water balance : When the water intake exceeds the output that means water is retained in the body is called positive water balance.

It occurs in the following conditions :

i. During growing period.
ii. Recovery from a disease.
iii. During pregnancy.
iv. Changes of dietary habits i.e. from high fatty acid to high protein diet.

Negative water balance : When water output exceeds the water intake, it is called negative water balance.

It occurs in the following conditions :

i. Vomittig, diarrhoea and haemorrhage.
ii. Burns.
iii. Excessive salivation like peptic ulcer, creatinism.
iv. When intake of fluid is restricted e.g starvation, narvosa, anorexia.
v. Unconscious state e.g. cerebrovascular accident.
vi. Addision's diseases, diabeties, hypofunction of adrenal gland.

Regulation of water balance

Water balance of the body are controlled by the following factors :

1. *Thirst mechanism :* Slight fall in blood volume or ECF volume causes osmosis of water out of the neural cells of the thirst center, thus shrinking the cell, causes drinking to maintain water balance. Intracellular dehydration, dryness of mouth cavity also stimulate thirst center thus increases water intake.
2. *Condition of kidney :* Kidney is the main regulator of the homeostasis of body fluid. According to situation and by excreting either dilute or concentrated urine kidney maintain water balance.
3. *Temperature and humidity :* Rise of temperature and

humidity incerases loss of water through the skin and respiratory tract. The thermoregulatory mechanism helps to steady the temperature and so indirectly maintain water balance.

4. *Endocrine glands :*
   i. Adrenal gland : It secretes aldosterone that by regulating the salt absorption from kidney also helps to maintain water balance.
   ii. ADH of posterior pituitary plays an important role in water balance by maintaining the reabsorption of water from kidney.
5. *Hypothalamus :* Supraoptic nuclei of anterior hypothalamus contain osmoreceptors. When osmolarity in the ECF rises, water pulls out of the osmoreecptors causing them to shrink and increasing their rate of discharge and maintain water balance through ADH.

Factors affecting water balance

1. Thirst mechanism
2. Condition of kidney
3. Temperature & humidity
4. Endocrine glands
5. Hypothalamus
6. Electrolyte and water balance
7. Diet.

Body Fluid

Water of the body together with its dissolved solute is called body fluid. It plays an important role in the basic physiology of body function. Most of the cellular reaction occurs in the fluid media. Water is the essential constituents of the body fluid and constitute about 57% of body weight in 70 kg adult male and 51% in adult female. In new born it is about 75%.

Types of body Fluid

1. *Intracellular fluid (ICF) :* The fluid inside the cells of the body is known as intracellular fluid. It constitutes about 40% of total body weight.
   The total amount of ICF = 28 liters.
2. *Extra cellurlar fluid (ECF) :* The fluid in the spaces out side the cells of the body known as extracellular fluid. It includes both the interstitial fluid that circulates in the spaces between the cells and also fluid of the blood plasma. It constitutes about 20% of total body weight.
   The total amount of ECF = 14 liters.

Body fluid compartments

The body fluid is mainly distributed between two compartments

1. *Intracellular fluid compartment :* It is the sumtotal of the fluid content of all cells of the body. It is about 28 liters.
2. *Extracellular fluid compartment :* It is the fluid out side of the cell. It is about 14 litres.
   The extracellular fluid in turn is divided into the *interstitial fluid* and blood *plasma.*
3. There is another small compartment of fluid that is referred to as ***transcellular fluid.*** It is usually considered to be a specialized type of extracellular fluid, although in some cases, its composition may differ markedly from that of plasma or interstitial fluid. It constitutes about 1 to 2 liters.This compartments includes fluids-
   i. Synovial fluid
   ii. Peritonial fluid
   iii. Pericardial fluid
   iv. Intraocular fluid
   v. Cerebrospinal fluid.

(Ref. Guyton & Hall-11th Edition, Page-292)

% of total body fluid compartments

Total body water (42 litre or) 60%

a. *Intracellular component* of body water (28 litres or) 40%

b. *Extracellualr component* of body water (14 litres) 20%

i. 25% of the extracellular component is in the vascular system-(*plasma*-3 litres) 5%

ii. 75% of the extracellular component is in the outside of blood vessels (*Interstitial fluid*) 15%

(Total blood volume is about 8% of body weight.)

(Ref. Ganong 22th Edition; Page-01)

iii. *Transcellular fluid : 1 to 2 litres*
(This compartment includies- fluid in the synovial, peritonial, pericardial, and intraoccular spaces, as well as the cerebrospinal fluid).

N.B. In the average 70-kilogram adult human, the total body water is about 60% of the body weight, or about 42 liters. This percentage can change, depending on age, sex, and degree of obesity. As a person grows older, the percentage of total body weight that is fluid gradually decreases. This is due in part to the fact that aging is usually associaed with an increased percentage of the body weight that is fat, which in turn decreases the percentage of water in the body. Because women normally have more body fat than men, they contain slightly less water than men in proportion to their body weight. Therefore when discussing the *average body fluid* compartments, we should realize that variations exits, depending on age, sex, and percentage of body fat.

(Ref. Guyton & Hall-11th Edition, Page-293)

ECF is more important than ICF- Explain

ECF is called "internal enviornment of the body" and it is more important than that of ICF. Because its constituents are accurately regulated so that the cells remain bathed continually in a fluid containing the proper electrolytes and nutrients for continued cellular function.

Important constituent of extracellular fluid :

Extracellular fluid, including the plasma and the interstitial fluid, contains large amounts of sodium and chloride ions, reasonably large amounts of bicarbonate ions, but only small quantities of potassium, calcium, magnesium, phosphate, and organic acid ions.

The composition of extracellular fluid is carefully regulated by various mechanisms but especially by the kidneys. This allows the cells to remain continually bathed in a fluid that contains the proper concentration of electrolytes and nutrients for optimal cell function.

Ionic composition of plasma and interstitial fluids are : Because the plasma and interstitial fluids are separated only by highly permeable capillary membranes, their ionic compositions are similar. The most important difference between these two compartments is the higher concentration of protein in the plasma; the capillaries have a low permeability to the plasma proteins and, therefore, leak only small amounts of proteins into the interstitial spaces in most tissues.

Because of the Donnan effect, the concentration of positively charged ions (cations) is slightly greater (about 2 per cent) in the plasma than in the interstitial fluid; this effect is the following: the plasma proteins have a net negative charge and, therefore, tend to bind cations, such as sodium and potassium ions, thus holding extra amounts of these cations in the plasma along with the plasma proteins. Conversely, negatively charged ions (anions) tend to have a slightly higher concentration in the interstitial fluid, compared with the plasma, because the negative charges of the plasma proteins repel the negatively charged anions. For practical purposes, however, the concentrations of ions in the interstitial fluid and plasma are considered to be equal.

(Ref. Guyton & Hall-11th Edition, Page-293)

Important constituents of the intracellular fluid :

The intracellular fluid is separated from the extracellular fluid by a selective cell membrane that is highly permeable to water but not to most of the electrolytes in the body.

In contrast to the extracelluiar fluid, the intracellular fluid contains only small quantities of sodium and chloride ions and *almost no calcium ions*. Instead, it contains large amounts of potassium and phosphate ions plus moderate quantities of magnesium and sulfate ions, all of which have low concentrations in the extracellular fluid. Also, cells contain large amounts of protein, almost four times as much as in the plasma. *(Ref. Guyton & Hall-11th Edition, Page-293)*

Difference between ECF and ICF

ECF	*ICF*
1. ECF contains large amount of sodium, chloride and bicarbonate ions plus nutrients for the cells such as oxygen, glucose, aminoacids and fatty acids.	1. ICF contain large amount of potassium, magnesium & phosphate ions.
2. It is needed for the maintenance of cellular function and called the internal environment of the body or milieu interior.	2. It is not called so.
3. Small amount of protein present in the the ECF.	3. Large amount of protein in ICF.

Osmolar substances in plasma extracellular fluid (ECF) and intracellular fluid (ICF)

	Plasma (mosm/liter of H_2O)	*Interstitial (mosm/liter of H_2O)*	*Intracellular (mosm/liter of H_2O)*
Na^+	*142*	139	14
K^+	4.2	4	*140*
Ca^{++}	1.3	1.2	0.001
Mg^{++}	0.8	0.7	20
Cl^-	*108*	108	4
HCO_3^-	24	28.3	10
HPO_4^- /$H_2PO_4^-$	2	2	*11*
SO_4^-	0.5	0.5	1
Phosphocreatine	-	-	45
Carnosine	-	-	14
Amino acids	2	2	8
Creatine	0.2	0.2	9
Lactate	1.2	1.2	1.5
Adenosine triphosphate	-	-	5
Hexose monophosphate	-	-	3.7
Glucose	5.6	5.6	-
Protein	1.2	0.2	4
Urea	4	4	4
Others	4.8	3.9	10
Total mOsm/liter	301.8	300.8	301.2
Corrected osmolar activity (mOsm/liter)	282.0	281.0	281.0

Total osmotic pressure at 37°C (mm Hg)	*5443*	*5423*	*5423*

(Ref. Guyton & Hall-11th Edition, Page-294)

Principle for measuring body fluid

The volume of any fluid compartment of the body can be measured by placing a substance in the compartment, allowing it to disperse evenly throughout the fluid, and then measuring the extent to which the substance become diluted. Then a sample of the dispersed fluid is removed and the concentration of the substance is analyzed. The volume of the fluid compartment can then measured from the following formula :

$$\text{Volume} = \frac{\text{Quantity of the test substancce instilled}}{\text{Concentration per ml of dispersed fluid}}$$

$$= \frac{\text{Volume x concentration of the test substancce injected}}{\text{Concentration per ml of dispersed fluid}}$$

This method can be used to measure the volume of virtually any compartment in the body as long as- *i. the indicator disperses evenly throughout the compartment, ii. the indicator disperses only in the compartment that is being measured, and iii. the indicator is not metabolized or excreted.* Several substances can be used to measure the volume of each of the different body fluids.

Determination of volumes of specific body fluid compartments

Measurement of body fluid volumes :

Volume	*Indicators*
Total body water	$^{3}H_20$, $^{2}H_20$, antipyrine
Extracellular fluid	^{22}Na, ^{125}I-iothalamate, thiosulfate, inulin
Intracellular fluid	(Calculated as Total body water- ECF)
Plasma volume	^{125}I-albumin, Evans blue dye (T-1824)
Blood volume	^{51}Cr-labeled red blood cells, or calculated as Blood volume = plasma volume/(1 - hematocrit)
Interstitial fluid	(Calculated as ECF - Plasma volume)

(Ref. Guyton & Hall-11th Edition, Page-296)

Measurement of total body water

Indicators : Radioactive water (tritium, $^{3}H_20$) or heavy water (deuterium, $^{2}H_2O$) and antipyrine can be used to measure total body water. Antipyrine, which is very lipid soluble and can rapidly penetrate cell membranes and distribute itself uniformly throughout the intracellular and extracellular compartments.

Procedure : Radioactive water (tritium, $^{3}H_20$) or heavy water (deuterium, $^{2}H_2O$) mix with the total body water within a few hours after being injected into the blood, and the dilution principle can be used to calculate total body water.

Total body water-

$$= \frac{\text{Volume x concentration of the test substancce injected}}{\text{Concentration per ml of dispersed fluid}}$$

(Ref. Guyton & Hall-11th Edition, Page-295)

Example : Suppose 100 ml of D_2O in isotonic saline is injected intravenously to a man of weighting about 70 kg. After an equilibirium of 2 hours, the plasma samples is analysed and D_2O concentration is found to be 0.0023 mosm/liter. During the period of equilibrium it is found to have a loss of average 0.5% of the quantitity adminstered. So, the volume of the distribution will be-

$$= \frac{\text{Quantity administered - Quantity excreted}}{\text{Equilibrium concentration}}$$

$$= \frac{100 - 0.5}{0.0023}$$

$$= \frac{99.5}{0.0023}$$

= 43260 ml

= 43.26 liter.

Measurement of extracellular fluid volume

Indicators : The volume of extracellular fluid can be estimated using any of several substances that disperse in the plasma and interstitial fluid but do not readily permeate the cell membrane. They include radioactive sodium, radioactive chloride, radioactive iothalamate, thiosulfate ion, and inulin.

Procedure : When any one of these substances (indicators) is injected into the blood, it usually disperses almost completely throughout the extracellular fluids within 30 to 60 minutes and the dilution principle can be used to calculate the extracellular fluid volume.

Extracellular fluid volume -

$$= \frac{\text{Volume x concentration of the indicator injected}}{\text{Concentration per ml of dispersed fluid}}$$

Some of these substances, however, such as radioactive sodium, may diffuse into the cell in small amounts. Therefore, one frequently speaks of the *sodium space*, or the *inulin space* instead of calling the measurement the true extracellular volume.

(N.B. Short notes on Na- Space)

(Ref. Guyton & Hall-11th Edition, Page-296)

Calculation of intracellular volume

The intracellular volume cannot he measured directly. However, it can be calculated as-

inward through the capillary membrane when pif is positive but outward when pif is negative.

True Interstitial fluid pressure :

In loose subcutanous tissue is = -3 mm Hg.

In tightly encased tissue i.e the pressure under- neath with tight fibrous fascial coverings are always more positive.

The plasma colloidal osmotic pressure : Which tends to cause osmosis of fluid inward through the membrane. It is about 28 mm of Hg.

The interstitial fluid colloidal osmotic pressure : Which tends to cause osmosis of fluid outward through the membrane. It is about 8 mm of Hg.

(Ref. Guyton & Hall-11th Edition, Page 185)

Forces causing filtration at the arterial end of the capillary

The approximate average forces operating at the arterial end of the capillary that cause movement through the capillary membrane are

a. *Forces tending to move fluid outward :*
   i. Capillary hydrostatic pressure 30 mm of Hg.
   ii. Negative interstitial free fluid pressure (-)3mm Hg *(i.e. Outward force 3 mm of Hg).*
   iii. Interstitial fluid colloidal osmotic pressure 8 mm Hg.

   Total outward force = 41 mm Hg. (30 + 3 + 8 =41 mm Hg).

b. *Forces tending to move fluid inward :*
   i. Plasma colloidal osmotic pressure 28 mm Hg.

   Total inward force = 28 mm Hg.

Summation of forces :

i. Out ward forces = 41 mm Hg
ii. In ward forces = 28 mm Hg.

Net out ward force = 13 mm Hg (41 - 28 = 13 mm of Hg).

This 13 mm Hg filtration pressure causes on the average about 0.5 percent of the plasma to filter out of the arterial end of the capillaries into the interstitial spaces.

(Ref. Guyton & Hall-11th Edition, Page 189)

Force causing reabsorption of fluid at the venous end of the capillary

The low pressure at the venous end of the capillary changes the balance of forces infavour of absorption as follows :

a. *Forces tending to move fluid inward :*
   i. Plasma colloidal osmotic pressure 28 mm Hg.
   Total inward force = 28 mm of Hg.

b. *Forces tending to move fluid outward :*
   i. Capillary pressure : 10 mm of Hg.
   ii. Negative interstitial free fluid pressure : (-)3 mm of Hg (i.e Outward force 3 mm of Hg).
   iii. Interstital fluid colloid osmotic pressure : 8 mm Hg.

   Total outward force : 21 mm of Hg (10+3+8 mm Hg)

Summation of forces :

i. Inward force : 28 mm Hg.
ii. Outward force : 21 mm Hg.

Net inward force = 7 mm of Hg (28 - 21 = 7 mm of Hg).

Thus the force that causes fluid to move into the capillary, 28 mm of Hg, is greater than that opposing reabsorption, 21 mm Hg. The difference, 7 mm of Hg is the reabsorption pressure. This reabsorption pressure. (7 mm Hg) draws the fluid from the tissue space into the venous end of the capillary.

(Ref. Guyton & Hall-11th Edition, Page 189)

Factors responsible for fluid exchange between the blood capillaries and intestitial space

The exchanges of fluid between plasma and the tissue spaces (interstitial spaces), both ways is a continuous process. The exchange has been considered to be due to the operation of the following factors :

1. *Capillary membrane and its permeability :*
   a. Lipid soluble materials through the cells
   b Lipid insoluble materials through the pores.
   c. Large molecular substances like protein dextran etc. through pinocytosis.
2. Diffusion
3. Filtration
4. Absorption
5. Metabolic activity of the tissue.

Interstitium and interstitial fluid

About one sixth of the body consists of spaces between cells, which collectively are called the *interstitium.* The fluid in these spaces is the *interstitial fluid.*

a. *Structure of the interstitium* : It has two major types of solid structures :
   i. *Collagen fiber bundles* : The collagen fiber bundles extend long distances in the interstitium.

   Function : They are extremely strong and therefore provide most of the tensional strength of the tissues.
   ii. *Proteoglycan filaments* : The proteoglycan filaments, however, are extremely thin, coiled molecules composed of about 98 per cent hyaluronic acid and 2 per cent *protein.* These molecules are so thin that they can never be seen with a light microscope and are difficult to demonstrate even with the electron microscope. Nevertheless, they form a mat of very fine reticular filaments aptly described as a *brush pile.*

Intracellular volume = Total body water - Extracellular volume.

(Ref. Guyton & Hall-11th Edition, Page-296)

Measurement of Plasma volume

Indicators Used : Plasma volume can be measured by using indicators are-

1. Evans blue dye (also called, T-1824)
2. Serum albumin labelled with radio-active iodine (^{125}I-albumin).

(Ref. Guyton & Hall-11th Edition, Page-296)

Procedure : Suppose 10 ml of venous blood of a subject is taken in a heparinized tube. This serves as the control sample. 5 ml of a 5% solution of Even's blue (T-1824) in diluted water is then injected intravenously. 10 minute after the injection another 10 ml of sample is withdrawn from the vein into another heparinized tube. The haematocrit of both sample are determined. The optical density of the dye stained plasma is estimated. 0.01 ml of the dye is then diluted to 5 ml (dilution is 1 : 500) with the control plasma and its optical density is measured.

So plasma volume (ml)

= Dye solution injected x dye Solution stadarisation

$$\times \frac{\text{Density of standard}}{\text{Density of unknown}}$$

Calculation of interstitial fluid volume

Interstitial fluid volume cannot be measured directly but it can be calculated as-

Interstitial fluid volume = Extracellular fluid volume - Plasma volume

Measurement of blood volume

The avreage blood volume of a normal adult man is approximately 5,000 ml. On the average approximtely 3000 ml of this is plasma and remainder 2000 ml is blood cells.

Here plasma volume is obtained same as ECF.

$$\text{Total blood volume} = \frac{\text{Plasma volume}}{1 - \text{Hematocrit}}$$

For example, if plasma volume is 3 liters and hematocrit is 0.40, then total blood volume would be calculated as

$$\text{Total blood volume} = \frac{3}{1 - 0.40}$$

$$= 5 \text{ liters}$$

Another way to measure blood volume is to inject into the circulation red blood cells that have been labeled with radioactive material. After these mix in the circulation, the radioactivity of the mixed blood sample can be measured, and the total blood volume can be calculated using the dilution principle. A substance frequently used to label the red blood cells is radio-active chromium (^{51}Cr), which binds tightly with the red blood cells.

(Ref. Guyton & Hall-11th Edition, Page-296)

Criteria of indicator used for measuring body fluid :

1. The indicator must mix with the volume of fluid within reasonable time.
2. It is not changed in anyway in the body.
3. It must be non-toxic.
4. It should be excreted in the urine within reasonable period.

Criteria of indicator used for measuring body water :

i. It must not be toxic.

ii. It is distributed through out the body water compartments and then diffuses readily across the cell membrane.

Q. 00. *Why Evan's blue and radioactive substances are choosen for plasma volume measurement?*

Ans. It is used because it is :

i. Must not be toxic

ii. Must not alter plasma volume

iii. Must not easily pass into tissue or be excreted

iv. Must not be taken up by the phagocytic cell of the blood.

Lean body mass

Lean body mass is that mass of the body which can be determined by substrating the fat content of body from the total body weight.

Lean body mass = total body weight - its fat content.

Measurment of lean body mass : Lean body mass can be calculated from the specific gravity of the subject determined by weighting the subject in air divided by the weight of displaced water.

Effective Filtration Pressure

It is the net filtration pressure that operating the filtration at the arterial or venous end.

Factors affecting the effective filtration pressure :

It depends upon :

i. Capillary pressure.

ii. Interstitial fluid pressure.

iii. Plasma colloidal osmotic pressure.

iv. Interstitial fluid colloidal osmotic pressure.

The capillary pressure (p_c) : Which tends to force fluid outward through the capillary membrane. It is averaging about 17 mm of Hg *(Indirect functional measurement, Direct cannulation of the capillaries averaging about 25 mm of Hg).*

The interstitial fluid pressure (p_f) : Which tends to force fluid

b. ***Gel in the interstitium*** : The fluid in the interstitium is derived by filtration and diffusion from the capillaries. It contains almost the same constituents as plasma except for much lower concentrations of proteins because proteins do not pass outward through the pores of the capillaries with ease. The interstitial fluid is entrapped mainly in the minute spaces among the proteoglycan filaments. This combination of the proteoglycan filaments and the fluid entrapped within them has the characteristics of a *gel* and therefore is called *tissue gel.*

Because of the large number of proteoglycan filaments, it is difficult for fluid to flaw easily through the tissue gel. Instead, it mainly diffuses through the gel; that is, it moves molecule by molecule from one place to another by kinetic motion rather than by large numbers of molecules moving together.

Diffusion through the gel occurs about 95 to 99 per cent as rapidly as it does through free fluid. For the short distances between the capillaries and the tissue cells, this diffusion allows rapid transport through the interstitium not only of water molecules but also of electrolytes, small molecular weight nutrients, cellular excreta, oxygen, carbon dioxide, and so forth.

(Q. What is the importance of the proteoglycan in preventing rapid flow of fluid in the tissue spaces?)

c. ***Free fluid in the interstitium*** : Although almost all the fluid in the interstitium normally is entrapped within the tissue gel, occasionally small *rivulets of free fluid* and *small free fluid vesicles* are also present, which means fluid that is free of the proteoglycan molecules and therefore can flow freely. When a dye is injected into the circulating blood, it often can be seen to flow through the interstitium in the small rivulets, usually coursing along the surfaces of collagen fibers or surfaces of cells. The amount of *free fluid* present in *normal* tissues is slight, usually much less than 1 per cent. Conversely, when the tissues develop edema, these small pockets and rivulets of free fluid expand tremendously until one half or more of the edema fluid becomes freely flowing fluid independent of the proteoglycan filaments.

(Ref. Guyton & Hall-11th Edition; page 184)

Function of the interstitial fluid

1. It constitute the internal medium in which the tissue cells are bathed. The cells draw O_2 and nutrition from the tissue fluid and excrete their metabolites into it. Hence, tissue fluid may be regraded as the medium which supplies all the immediate requirements of the cells.
2. It acts as a great reservior of water, salts, nutrition etc.
3. It maintain the turgescence of the connective tissue and the skin.
4. The tissue fluid in some cases afford protection and maintain shape of the structure.

Quantity of plasma that filters out of the capillary

0.5 percent of the plasma fluid that filters out of the arterial ends of the capillaries flow through the tissue spaces to the venous ends of the capillaries, where 9/10th flows into the lymphatic capillaries.

(Ref. Guyton & Hall-11th Edition)

Volumes and osmolalities of extracellular & intracellular fluid in abnormal states

Some of the different factors that can cause extracellular and intracellular volumes to change markedly are-

1. Ingestion of water
2. Dehydration
3. Intravenous infusions of different types of solutions.
4. Loss of large amounts of fluid from the gastrointestinal tract.
5. Loss of abnormal amounts of fluid by sweating or through the kidneys.

One can calculate both the changes in intracellular and extracellular fluid volumes and the types of therapy that should be instituted if the following basic principles are kept in mind :

1. *Water moves rapidly across cell membranes*; therefore, the osmolarities of intracellular and extracellular fluids remain almost exactly equal to each other except for a few minutes after a change in one of the compartments.
2. *Cell membranes are almost completely impermeable to many solutes*; therefore, the number of osmoles in the extracellular or intracellular fluid remains constant unless solutes are added to or lost from the extracellular compartment.

With these basic principles in mind, we can analyze The effects of different abnormal fluid conditions on extracellular and intracellular fluid volumes and osmolarities.

(Ref. Guyton & Hall-11th Edition, Page 299)

Saline solution

Effect of adding saline solution to the extacellular fluid : If an *isotonic saline solution* is added to the extracellular fluid compartment, the osmolarity of the extracellular fluid does not change; therefore, no osmosis occurs through the cell membranes. The *only effect is an increase in extracellular fluid volume*. The sodium and chloride largely remain in the extracellular fluid because the cell membrane behaves as though it were virtually impermeable to the sodium chloride.

If a *hypertonic solution* is added to the extracellular fluid, the extracellular osmolarity increases and causes osmosis of water out of the cells into the extracellular compartment. Again, almost all the added sodium chloride remains in the extracellular compartment, and fluid diffuses from the cells into the extracellular space to achieve osmotic equilibrium. *The net effect is an increase in extracellular volume (greater*

than the volume of fluid added), a decrease in intracellular volume, and a rise in osmolarity in both compartments.

If a *hypotonic solution* is added to the extracellular fluid, the osmolarity of the extracelluiar fluid decreases and some of the extracellular water diffuses into the cells until the intracellular and extracellular compartments have the same osmolarity (Figure 25-6C): *Both the intracellular and the extracellular volumes are increased by addition of hypotonic fluid, although the intracellular volume increases to a greater extent.*

(Ref. Guyton & Hall-11th Edition, Page 299)

Calculation of fluid shifts and osmolarities after infusion of hypertonic saline : We can calculate the sequential effects of infusing different solutions on extracellular and intracellular fluid volumes and osmolarities. ***For example***, *if we infuse 2 liters of a hypertonic 2.9 per cent sodium chloride solution into the extracellular fluid compartment of a 70-kilogram patient whose initial plasma osmolarity is 280 mOsm/L*, what would be the intracellular and extracellular fluid volumes and osmolarities after osmotic equilibrium?

1. The *first step* is to calculate the initial conditions, including the volumes, concentrations, and total milliosmoles in each compartment. Assuming that extracellular fluid volume is 20 per cent of body weight and intracellular fluid volume is 40 per cent of body weight. the following volumes and concentrations can he calculated.

Step 1. Initial conditions :

	Volumes (Liters)	*Concentration (mOsml/L)*	*Total (mOsm)*
Extracellular fluid	14	280	3920
Intracellur fluid	28	280	7840
Total body fluid	42	280	11,760

Next, *we calculate the total milliosmoles added to the extracellular fluid in 2 liters of 2.9 per cent sodium chloride*. A 2.9 per cent solution means that there are 2.9 g/100 ml, or 29 grams of sodium chloride per liter. Because the molecular weight of sōdium chloride is about 58 g/mol, this means that there is about 0.5 mole of sodium chloride per liter of solution. For 2 liters of solution, this would be 1 mole of sodium chloride. Because 1 mole of sodium chloride is about equal to 2 osmoles (sodium chloride has two osmotically active particles per mole), *the net effect of adding 2 liters of this solution is to add 2000 milliosmoles of sodium chloride to the extracellular fluid.*

2. In *Step 2, we calculate the instantaneous effect of adding 2000 milliosmoles of sodium chloride to the extracellular fluid along with 2 liters of volume* : Instantineously, there would be no change in the *intracellular fluid* concentration or volume, and there would be no osmotic equilibrium. In the *extracellular fluid*, however, there would be an additional 2000 milliosmoles of total solute, yielding a total of 5920 milliosmoles. Because the extracellular compartment now has 16 liters of volume, the concentration can be calculated by dividing 5920 milliosmoles by 16 liters to yield a concentration of 370 rnOsmol/L. Thus, the following values would occur instantly after adding the solution.

Step 2. Instantaneous effect of adding 2 liters of 2.9 per cent sodium chloride :

	Volumes (Liters)	*Concentration (mOsml/L)*	*Total (mOsm)*
Extracellular fluid	16	370	5920
Intracellur fluid	28	280	7840
Total body fluid	44	No equilibrium	13,760

3. In the *third step*, we *calculate the volumes and concentrations that would occur within a few minutes after osmotic equilibriurn develops* : In this case, the concentration is in the intracellular and extracellular fluid compartments would be equal and can be calculated by dividing the total milliosmoles in the body, 13,760, by the total volume, which is now 44 liters. This yields a concentration of 312.7 mOsm/L. Therefore, all the body fluid compartments will have this same concentration after osmotic equilibrium. Assuming that no solute or water has been lost from the body and that there is no movement of sodium chloride into or out of the cells, *we then calculate the volumes of the intracellular and extracellular compartments* : the *intracellular fluid volume* is calculated by dividing the total milliosmoles in the intracellular fluid (7840) by the concentration (312.7 mOsm/L) to yield a volume of 25.1 liters. *Extracellular fluid volume* is calculated by dividing the total milliosmoles in extracellular fluid (5920) by the concentration (312.7 mOsm/L) to yield a volume of 18.9 liters. Again, these calculations are based on the assumption that the sodium chloride added to the extracellular fluid remains there and does not move into the cells.

Step 3. Effect of adding 2 liters of 2.9 per cent sodium chloride after osmotic equilibrium :

	Volumes (Liters)	*Concentration (mOsml/L)*	*Total (mOsm)*
Extracellular fluid	18.9	312.7	5920
Intracellur fluid	25.1	312.7	7840
Total body fluid	44.0	312.7	13,760

Thus, one can see from this example that adding 2 liters of a hypertonic sodium chloride solution causes a 4.9 liter increase in extracellular fluid volume while decreasing intracellular fluid volume by 2.9 liters.

This method of calculating changes in intracellular and extracellular fluid volumes and osmolarities can be applied to virtually any clinical problem of fluid volume regulation. An understanding of the mathematical aspects of osmotic equilibria between intracellular and extracellular fluid compartments is essential for understanding almost all fluid abnormalities of the body and their treatment.

(Ref. Guyton & Hall-11th Edition, Page 299, 300)

Glucose and other solutions administered for nutritive purposes :

Many types of solumions are administered intravenously to provide nutrition to people who cannot otherwise take adequate amounts of nutrition. *Glucose solutions* are widely used, and *amino acid* and *homogenized fat solutions* are used to a lesser extent. When These solutions are administered, their concentrations of osmotically active substances are usually adjusted nearly to isotonicity or they are given slowly enough that they do not upset the osmotic equilibria of the body fluids. After the glucose or other nutrients are metabolized, an excess of water often remains, especially if additional fluid is ingested. Ordinarily, the kidneys excrete this in the form of a very dilute urine. The net resull is, therefore, addition only of the nutrients to the body.

(Ref. Guyton & Hall-11th Edition, Page 301)

Clinical abnormalities of fluid volume regulation : Hyponatremia and Hypernatremia

The primary measurement that is readily available to the clinician in evaluating a patient's fluid status often is the plasma sodium concentration. Plasma osmolarity is not routinely measured but because sodium and its associated anions (mainly chloride) account for more than 90 per cent of the solute in the extracellular fluid, plasma sodiurn concentration is a reasonable indicator of plasma osmolarity under many conditions.

When plasma sodium concentration is reduced below normal (about 142 mEq/L), a person is said to have *hyponatrernia.*

When plasma sodium concentration is elevated above normal, a person is said to have *hypernatremia.*

(Ref. Guyton & Hall-11th Edition, Page 301)

Causes of hyponatremia : Excess water or loss of sodium.

Decreased plasma sodium concentration can result from loss of sodium chloride from the extracellular fluid or addition of excess water to the extracellular fluid. A primary loss of sodium chloride usually results in *hypo-osmotic dehydration* and is associated with decreased extracellular fluid volume. Conditions that can cause *hyponatremia owing to loss of sodium chloride include diarrhea and vomiting. Overuse of diuretics* that inhibit the ability of the kidneys to conserve sodium and *certain types of sodium-wasting kidney diseases* can also cause modest degrees of hyponatremia. Finally, *Addison's disease*, which results from decreased secretion of the hormone aldosterone, impairs the ability of the kidneys to reabsorb sodium and can cause a modest degree of hyponatremia.

Hyponatremia can also be *associated with excess water retention*, which dilutes the sodium in the extracellular fluid, a condition that is referred to as *hypo-osmotic overhydration*. For example, excessive secretion of antidiuretic hormone, which causes the kidney tubules to reabsorb more water, can lead to hyponatremia and overhydration.

(Ref. Guyton & Hall-11th Edition, Page 301)

Causes of hypernatremia : Water loss or excess sodium.

Increased plasma sodium concentration, which also causes increased osmolarity, can be due either to loss of water from the extracellular fluid, which concentrates the sodium ions, or to an excess of sodium in the extracellular fluid. When there is primary loss of water from the extracellular fluid, this results in *hyperosmotic dehydration*. This condition can occur from an inability to secrete antidiuretic hormone, which is needed for the kidneys to conserve water. As a result of lack of antidiuretic hormone, the kidneys excrete large amounts of dilute urine (a disorder referred to as diabetes insipidus), causing dehydration and increased concentration of sodium chloride in the extracellular fluid. In certain types of renal diseases, the kidneys cannot respond to antidiuretic hormone, also causing a type of *nephrogenic diabetes insipidus*. A more common cause of hypernatremia associated with decreased extracellular fluid volume is dehydration caused by a water intake that is less than the water lost from the body, as can occur with sweating during heavy exercise.

Hypernatremia can also occur as a result of excessive sodium chloride added to the extracellular fluid. This often result in *hyperosmotie overhydration* because excess extracellular sodium chloride is usually associated with at least some degree of water retention by the kidneys as well. For example, excessive secretion of the sodium-retaining hormone aldosterone can cause a mild degree of hypernatremia and overhydration. The reason that the hypernatremia is not more severe is that increased aldosterone secretion causes the kidneys to reabsorb greater amounts of water as well as sodium.

N.B. Thus, in analyzing abnormalities of plasma sodium concentration and deciding on proper therapy, one should first determine whether the abnormality is caused by a primary loss or gain of sodium or a primary loss or gain of water.

(Ref. Guyton & Hall-11th Edition, Page 302)

Extracellular volume depletion

Deficiency of H_2O and Na^+ causes shrinkase both of the interstitial space and of the blood volume. A simple water

deficit reduces the ECF and ICF proportionately. A NaCl deficit always decreases the ECF volume.

a. *Isosmotic volume depletion* : Only ECF volume decrease with no changes in osmolality. This is due to :
   i. Haemorrhage
   ii. Gastrointestinal fluid loss
      - vomiting
      - diarrhoea.
   iii. Fluid loss in burn.

ii. *Hyperosmotic volume depletion* : Both the ECF and ICF volume decrease with increased osmolality of both compartments. Common causes are:
   a. Inadequate intake
   b. Diabetes insipidus
   c. Diabetes mellitus
   d. Excessive sweating
   e. Fever.

iii. *Hyposmotic volume depletion* : It is characterized by decrease in ECF volume (ICF volume increases in this case) with decrease osmolality of both ECF and ICF compartment. *Causes are* :
   a. Renal loss of NaCI
   b. Addison's disease (decrease circulating aldosterone)

Effects of extraeellular volume depletion (dehydration)

Effects of extracellular volume depletion (i.e dehydration) are :

1. Increase thirst
2. Muscle cramps
3. Nausia and vomitting
4. Cold extremities (due to peripheral vasoconstriction)
5. Tachycardia
6. Loss of skin elasticity
7. Postural hypotension
8. Low jugular venous pressure
9. Arterial hypotension (a late sign).

Principle of management of extraeellular volume depletion

The overridden principle of treatment is aim to replace what is missing :

i. Hemorrhage : replace whole blood
ii. Loss of plasma : treat with human plasma or plasma substitute
iii. Loss of water and electrolytes : treat by replacement with water and electrolytes (as in vomiting and diarrhoea)

ORS

ORS is oral rehydreation solution.

i. *Composition of ORS* : The world health organization (WHO) oral rehydration solution is :
   a. Sodium : 90 mmol/litre
   b. Potassium : 20 mmol/litre
   c. Chloride : 80 mmol/litre
   d. Citrate : 10 mmol/litre
   e. Glucose : 111 mmol/litre.

ii. The presence of glucose in the ORS has been shown to promote electrolyte absorption

iii. *Indication* : Correction of mild to moderate dehydration.

Hypovolaemia

Physiological response to hypovolaemia : Hypovolaemia means decrease effective circulatory volume. Hypovolaemia may results from both the exogenous volume losses (i.e. haemorrhage, burn) and endogenous losses (i.e sepsis, anaphylaxis). Hypovolaemia cause shrinkage both of the interstitial space and of the blood volume and have profound effects on organ function. The physiological responses that become activated to counteract the hypovolaemie state and to maintain the normal homeostatic condition are :

i. *Sympatho-adrenal response to hypovolaemia* : Hypovolaeinia causes reduction in the effective circulatory volume that results in hypotension. Hypotension stimulates sympathetic nervous activity and increases release of catecholamines (i.e. epinephrine and norepinephrine) from the adrenal medulla which causes :
   a. Generalized vasoconstriction (except brain and heart)
   b. Increase myocardial contractility
   c. Increase heart rate.
   Vasoconstriction is more marked in the skin, where it accounts for the coolness and pallor.

ii. *Cardio-vascular response* : Hypovolaemia leads to decrease in circulatory volume and thus reduces venous return, cardiac output and blood pressure.
   In hypotension arterial baroreceptors are stressed to a lesser degree and sympathetic output is increased. The effect are :
   a. Reflex tachycardia
   b. Vasoconstriction → increased peripheral resistance
   c. Venous return improved → increase cardiac output
   d. Blood pressure rises to normal levels

iii. *Neuroendocrine response* : A 10%-20% decrease in blood volume will evoke ADH release. Other endocrine hormones released in response to hypovolaemia are :
   a. ADH : improves antidiuresis
   b. Cortisol : causes fluid retention
   c. Beta-endorphin : is responsible for some of the cardiovascular changes.

iv. *Renal response* : A low circulatory blood volume causes reduction in renal perfusion, which in turn stimulates the

juxtaglomerular apparatus to release renin and ultimately increases circulatory angiotensin II level. Angiotensin II stimulates secretion of aldosterone by the adrenal cortex which causes sodium and water retention from renal tubules. This helps to restore the circulatory volume.

Oedema

i. *Definition* : Oedema means accumulation of excess fluid in the tissue space (interstitial space).

ii. *Basic mechanism* : The basic mechanism for oedema formation is increased shift of salt and water into interstitium. This is result from:
   a. Increased ECF volume
   b. Decreased plasma colloid osmotic pressure
   c. Increased venous pressure
   d. Increased microcirculatory permeability.

   Peripheral oedema is caused by expansion of the extracellular volume by at least 2 liters (15%)

iii. *Types* :
   a. Oedema may be generalized or local.
   b. It may pitting (due to protein deficiency) and non-pitting in nature.

iv. *Causes of oedema are* :
   1. Conditions associated with generalized.oedema
      a. Cardiac failure
      b. Nephrotic syndrome
      c. Hepatic cirrhosis
      d. Protein losing enteropathy
      e. Thiamine deficiency
      f. Pregnancy
      g. Drugs : NSAIDs, nifedipine.
   2. Conditions associated with localized edema :
      a. Trauma
      b. Inflammation
      c. Thrombosis
      d. Prolong immobility.

Regulation of extracellular fluid composition & volume

Introduction : The major homeostatic mechanisms that operate, primarily through the kidneys and the lungs, to maintain the ***tonicity***, the ***volume***, and the ***specific ionic composition***, particularly the H^+ *concentration* of the ECF. The interstitial portion of this fluid is the fluid environment of the cells, and life depends upon the constancy of this 'internal sea".

(Ref. Ganong 22th Edition; Page-729)

Defense of tonicity

The defense of the tonicity of the ECF is primarily the function of the *vasopressin-secreting* and *thirst mechanisms*. The *total body osmolality is directly proportionate to the total body sodium plus the total body potassium divided by the total body water,* so that changes in the osmolality of the body fluids occur when there is a disproportion between the amount of these electrolytes and the amount of water ingested or lost from the body.

i. *When the effective osmotic pressure of the plasma rises-* vasopressin secretion is increased and the thirst mechanism is stimulated. Water is retained in the body, diluting the hypertonic plasma, and water intake is increased.

ii. *Conversely, when the plasma becomes hypotonic* - vasopressin secretion is decreased and 'solute-free water' (water in excess of solute) is excreted.

In this way, the tonicity of the body fluids is maintained within a narrow normal range. In health, plasma osmolality ranges from 280 to 295 mosml/kg of H_2O, with vasopressin secretion maximally inhibited at 285 mosm/kg and stimulated at higher values.

(Ref. Ganong 22th Edition; Page-729)

Defense of volume

The volume of the ECF is determined primarily by the total amount of osmotically active solute in the ECF. Since $Na^+$and $Cl^-$are by far the most abundant osmotically active solutes in ECF, and since changes in Cl^- are to a great extent secondary to changes in Na^+, the amount of Na^+ in the ECF is the most important determinant of ECF volume. Therefore, the mechanisms that control Na^+ balance are the major mechanisms defending ECF volume. There is, however, a volume control of water excretion as well; *a rise in ECF volume inhibits vasopressin secretion, and a decline in ECF volume produces an increase in the secretion of this hormone.* Volume stimuli override the osmotic regulation of vasopressin secretion. Angiotensin II stimulates aldosterone and vasopressin secretion. It also causes thirst and constricts blood vessels, which help to maintain blood pressure. Thus, angiotensin II plays a key role in the body's response to hypovolemia. In addition, expansion of the ECF volume increases the secretion of ANP and BNP by the heart, and this causes natriuresis and diuresis.

In disease states, loss of water from the body (dehydration) causes a moderate decrease in ECF volume, because water is lost from both the intracellular and extracellular fluid compartments; but loss of Na^+ in the *stools* (diarrhea), *urine* (severe acidosis, adrenal insufficiency), or *sweat* (heat prostration) decreases ECF volume markedly and eventually leads to shock. The immediate compensations in shock operate principally to maintain intravascular volume, but they also affect Na^+ balance. In adrenal insufficiency, the decline in ECF volume is due not only to loss of Na^+ in the urine but also to its movement into cells.

Because of the key position of Na^+ in volume homeostasis, it is

not surprising that more than one mechanism has evolved to control the excretion of this ion.

When ECF volume is decreased, blood pressure falls. Glomerular capillary pressure declines, and the GFR therefore falls, reducing the amount of Na filtered. Tubular reabsorption of Na^+ is increased, in part because the secretion of aldosterone is increased. Aldosterone secretion is controlled in part by a feedback system in which the change that initiates increased secretion is a decline in mean intravascular pressure. Other changes in Na^+ excretion occur too rapidly to be due solely to changes in aldosterone secretion. For example, rising from the supine to the standing position increases aldosterone secretion. However, Na^+ excretion is decreased within a few minutes. and this rapid change in Na^+ excretion occurs in adrenalectamized subjects. It is probably due to hemodynamic changes and possibly to decreased ANP secretion.

(*N.B. Regulation of Na^+*)

(Ref. Ganong 22th Edition; Page-729)

Nervous and hormonal factors increase the effective ness of renal-body fluid feedback control :

(Basic mechanism of controlling blood volume /control of extracellular fluid volume by the kidney) : The nervous and hormonal mechanisms usually act in concert with the pressure natriuresis and pressure diuresis mechanisms, making them more effective *in minimizing the changes in blood volume, extracellular fluid volume, and arterial pressure* that occur in response to day-to-day challenges. However, abnormalities of kidney function or of the various nervous and hormonal factors that influence the kidneys can lead to serious changes in blood pressure and body fluid volumes.

i. ***Sympathetic nervous system control of renal excretion*** : *The arterial baroreceptor and low-pressure stretch receptor reflexes :* Because the kidneys receive extensive sympathetic innervation, changes in sympathetic activity can alter renal sodium and water excretion as well as regulation of extracellular fluid volume under some conditions. *For example, when blood volume is reduced by hemorrhage-* the pressures in the pulmonary blood vessels and *other low-pressure regions of the thorax decrease, causing reflex activation of the sympathetic nervous system. This in turn increases renal sympathetic nerve activity, which has several effects to decrease sodium and water excretion- i. constriction of the renal arterioles, with resultant decreased GFR; ii. increased tubular reabsorption of salt and water; and iii. stimulation of renin release and increased angiotensin II and aldosterone formation, both of which further increase tubular reabsorption.* And if the reduction in blood volume is great enough to lower systemic arterial pressure, further activation of the sympathetic nervous system occurs because of decreased stretch of the arterial baroreceptors located in the carotid sinus and aortic arch.

All these reflexes together play an important role in the rapid restitution of blood volume that occurs in acute conditions such as hemorrhage. Also, reflex inhibition of renal sympathetic activity may contribute to the rapid elimination of excess fluid in the circulation that occurs after eating a meal that contains large amounts of salt and water.

(Ref.Guyton & Hall 11th Edition; Page 377)

ii. ***Role of Angiotensin II in controlling renaI excretion*** : One of the body's most powerful controllers of sodium excreion is angiotensin II. Changes in sodium and fluid intake are associated with reciprocal changes in angiotensin-II formation, and this in turn contributes greatly to the maintenance of body sodium and fluid balances. That is, when sodium intake is elevated above normal, renin secretion is decreased, causing decreased anglotensin II formation. Because angiotensin II has several important effects in increasing tubular reabsorption of sodium, a reduced level of angiotensit II decreases tubular reabsorption of sodium and water, thus increasing the kidneys' excretion of sodium and water. The net result is to minimize the rise in extracellulai fluid volume and arterial pressure that would otheryise occur when sodium intake increases.

Conversel., when sodium intake is reduced below normal, increased levels of angiotensin II cause sodium and water retention and oppose reductions in arterial blood pressure that would otherwise occur. Thus, changes in activity of the renin-angiotensin system act as a powerful amplifier of the pressure natriuresis mechanism for maintaining stable blood pressures and body fluid volume.

(Ref.Guyton & Hall 11th Edition; Page 377)

iii. ***Role of Aldosterone in controlling renal excretion*** : Aldosterone increases sodium reabsorption, *especially in the cortical collecting tubules.* The *increased sodium reabsorption is also associated with increased water reabsorption and potassium secretion.* Therefore, the net effect of aldosterone is to make the kidneys retain sodium and water but to increase potassium excretion in the urine.

The function of aldosterone in regulating sodium balance is closely related to that described for angiotensin II. That is, with reduction in sodium intake, the increased angiotensin II levels that occur stimulate aldosterone secretion, which in turn contributes to the reduction in urinary sodium excretion and, therefore, to the maintenance of sodium balance. Conversely, with high sodium intake, suppression of aldosterone formation decreases tubular reabsorption, allowing the kidneys to excrete larger amounts of sodium. Thus, changes in aldosterone formation also aid the pressure natriuresis mechanism in maintaining sodium balance during variauons in salt intake.

(Ref.Guyton & Hall 11th Edition; Page 378)

iv. ***Role of ADH in controlling renal water excretion*** : ADH plays an important role in allowing the kidneys to form a small volume of concentrated urine while excreting normal amounts of salt. This effect is especially important during water deprivation, which strongly elevates plasma levels of ADH that in turn increase water reabsorption by the kidneys and help to minimize the decreases in extracellular fluid volume and arterial pressure that would otherwise occur. Water deprivation for 24 to 48 hours normally causes only a small decrease in extracellular fluid volume and arterial pressure. However, if the effects of ADH are blocked with a drug that antagonizes the action of ADH to promote water reabsorption in the distal and collecting tubules, the same period of water deprivation causes a substantial fall in both extracellular fluid volume and arterial pressure.

Conversely, when there is excess extracellular volume, decreased ADH levels reduce reabsorption of water by the kidneys, thus helping to rid the body of the excess volume.

Excess ADH secretion usually causes only small increases in extracellular fluid volume but large decreases in sodium concentration.

(Ref.Guyton & Hall 11th Edition; Page 379)

v. ***Role of atrial natriuretic peptide in controlling renal excretion*** : Some researchers believe that several natriuretic hormones may also contribute to volume regulation. One of the most important of the natriuretic hormones is a peptide referred to as atrial natriuretic peptide (*ANP*), released by the cardiac atrial muscle fibers. The stimulus for release of this peptide appears to be overstretch of the atria, which can result from excess blood volume. *Once released by the cardiac atria, ANP enters the circulation and acts on the kidneys to cause small increases in GFR and decreases in sodium reabsorption by the collecting ducts. These combined actions of ANP lead to increased excretion of salt and water, which helps to compensate for the excess blood volume.*

(Ref.Guyton & Hall 11th Edition; Page 379)

N.B. ***Other hormones acting on Kidney***

Parathormone : It is secreted by the parathyroid gland.

i. It increases the renal tubular reabsorption of Ca^{++} ion.

ii. It increases the renal tubular secretion of pho phate.

Growth hormone : Secreted by the anterior pituitary. It acts upon kidney and caused the release of somatomedins from kidney. These somatomedins help in bone and cartilage growth.

Control of blood pressure by the kidney *(Renin angiotensin mechanism) :* Renin is synthesized and stored in an inactive form called prorenin in the juxtaglomerular cells of the kidneys. When the arterial pressure falls intrinsic reactions in the kidneys themselves cause many of these prorenin molecules to split and release renin. Most of the renin enters the blood.

Renin is an enzyme, not a vasoactive substance itself. It acts enzymatically on another plasma protein, a globulin called renin substrate (or angiotensinogen), to release a 10-amino acid peptide, angiotengin-I. The renin persist in the blood for 30 minutes to an hour and continues to cause formation of angiotensin-I during this entire time.

Within a few seconds after formation of the angiotensin-I, two additional amino acids are split from it to form the 8-amino acid peptide angiotensin-II, catalyzed by the converting enzyme, present in the endothelium of the lung vessels. However, it persists in the blood only for a minute or two because it is rapidly inactivated by multiple blood and tissue enzymes collectively called angiotensinase.

During its persistence in the blood, Angiotensin-II causes :

a. Intense vasoconstriction in the arterioles and, less extent in the vein.

b. Decrease the excretion of both salt and water, this increase the extracellular fluid volume.

Thus the blood pressure is increased.

(Ref. Guyton & Hall 11th Edition)

Defense of specific ionic composition

Special regulatory mechanisms maintain the levels of certain specific ions in the ECF as well as the levels of glucose and other nonionized substances important in metabolism. The feedback of Ca^{2+}on the parathyroids and the calcitonin-secreting cells to adjust their secretion maintains the ionized calcium level of the ECF. The Mg^{2+} concentration is subject to close regulation, but the mechanisms controlling Mg^{2+} metabolism are incompletely understood.

The mechanisms controlling Na^+ and K^+ content are part of those determining the volume and tonicity of ECF and are discussed above. The levels of these ions are also dependent upon the H^+concentration, and pH is one of the major factors affecting the anion composition of ECF.

(Ref. Ganong 22th Edition; Page-730)

Defense of H^+ concentation : The mystique that envelopes the subject of acid-base balance makes it necessary to point out that the core of the problem is not 'buffer base' or 'fixed cation' or the like but simply the maintenance of the H^+ concentration of the ECF. The mechanisms regulating the composition of the ECF are particularly important as far as this specific ion is concerned, because the machinery of the cells is very sensitive to changes in H^+ concentration. Intracellular H^+ concentration, which can be measured by using microelectrodes, pH-sensitive fluorescent dyes, and phosphorus magnetic resonance, is different from extracellular pH and appears to regulate a variety of intracellular processes. However, it is sensitive to changes in ECF H^+ concentration.

The pH notation is a useful means of expressing H^+

concentrations in the body, because the H^+ concentrations happen to be low relative to those of other cations. Thus, the normal Na^+ concentration of arterial plasma that has been equilibrated with red blood cells is about 140 meq!L, whereas the H^+ concentration is 0.00004 meq/L. The pH, the negative logarithm of 0.00004 is therefore 7.4. Of course, a decrease in pH of 1 unit, eg. from 7.0 to 6.0, represents a ten-fold increase in H^+ concentration. It is important to remember that the pH of blood is the pH of ***true plasma***- plasma that has been in equilibrium with red cells- because the red cells contain hemoglobin, which is quantitatively one of the most important blood buffers.

(Ref. Ganong 22th Edition; Page-730)

H^+ Balance : The pH of the arterial plasma is normally 7.40 and that of venous plasma slightly lower. Technically, acidosis is present whenever the arterial pH is below 7.40, and alkalosis is present whenever it is above 7.40, although variations of up to 0.05 pH unit occur without untoward effects. The H^+ concentrations in the ECF that are compatible with life cover an approximately 5-fold range, from 0.00002 meq/L (pH 7.70) to 0.0001 meq/L (pH 7.00).

H^+ concentration and pH of body fluid :

	H^+ concentration		*pH*
	meq/L	*mol/L*	
Gastric Hcl	150	0.15	0.8
Maximal urine acidity	0.03	3x10-5	4.5
Extreme acidosis	0.0001	1x10-7	7.0
Plasma Normal	0.00004	4x10-8	7.0
Extreme alkalosis	0.00002	2x10-8	7.0
Pancreatic juice	0.00001	1x10-8	8.0

(Ref. Ganong 22th Edition; Page-731)

Amino acids are utilized in the liver for gluconeogenesis, leaving as products NH_4^+ and HCO_3^- from their amino and carhoxyl groups. The NH_4^+ is incorporated into urea and the protons that are formed are buffered intracellularly by HCO_3^-, so little NH_4^+ and HCO_3^- escape into the circulation. However, metabolism of sulfur-containing amino acids produces H_2S0_4, and metabolism of phosphorylated amino acids such as phosphoserine produces H_3PO_4. These strong acids enter the circulation and present a major H^+ load to the buftérs in the ECF.

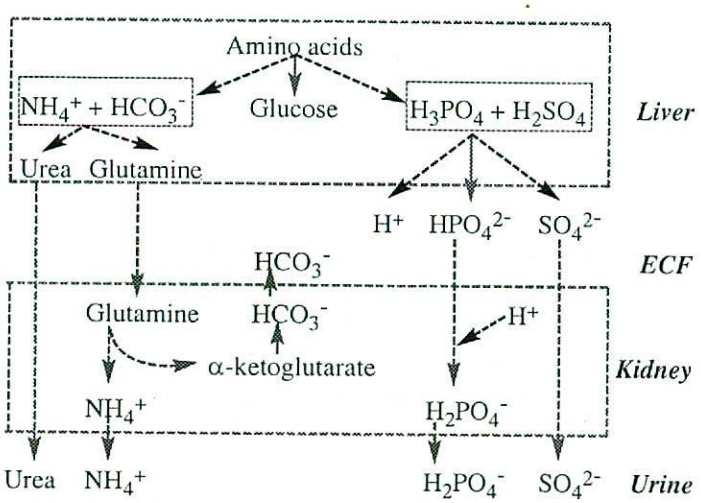
The H^+ load (causes of acdosis) from :

i. Amino acid metabolism is normally about 50 meq/day.
ii. The CO_2 formed by metabolism in the tissues is in large part hydrated to H_2CO_3 and the total H^+ load from this source is over 12,500 meq/day. However, most of the CO_2 is excreted in the lungs, and only small quantities of the H^+ remain to be excreted by the kidneys.
iii. Common sources of extra acid loads are-
   a. Strenuous exercise (lactic acid)
   b. Diabetic ketosis (acetoaeetic acid and beta-hydroxy butyric acid)
   c. Ingestion of acidifying salts such as NH_4CI and $CaCl_2$, which in effect add HC1 to the body.
   iv. Failure of diseased kidneys to excrete normal amounts of acid is also a cause of acidosis.

Causes of alkalosis : Fruits are the main dietary source of alkali. They contain Na^+ and K^+ salts of weak organic acids, and the anions of these salts are metabolized to CO_2, leaving $NaHCO_3$ and $KHCO_3$ in the body. $NaHCO_3$ and other alkalinizing salts are sometimes ingested in large amounts, but a *more common cause of alkalosis is loss of acid from the body as a result of vomiting of gastric juice rich in HCI.* This is of course equivalent to adding alkali to the body.

(Ref. Ganong 22th Edition; Page-731)

Role of the liver and kidneys in the handling of metabolically produced acids loads :



(Ref. Ganong 22th Edition; Page-731)

Directions : Write 'T' for true & 'F' for false against each of the following statement.

Q. 01. **Following are the ECF compartment :**
- T a. Plasma
- T. b. Pleural fluid
- T c. CSF
- T d. Synovial fluid
- T e. Peritonial fluid.

Q. 02. **Plasma concentration of ECF are as follows :**
- T a. Na^+ : 142 mEq/L
- T b. K^+ : 4 mEq/L
- T c. Ca^{++} : 2.4 mEq/L
- T d. Mg^{++} : 1.2 mEq/L
- T e. PO_2 : 35 mm of Hg.

Q. 03. **Plasma concentration of ICF are as follows**
- T a. Na^+ : 10 mEq/L
- T b. K^+ : 140 mEq/L
- T c. Ca^{++} : 0.0001 mEq/L
- T d. Mg^{++} : 58 mEq/L
- T e. PO_2 : 20 ?mm of Hg.

Q. 04. **Plasma concentration of the ECF are as follows :**
- T a. Cl^- : 103 mEq/L
- T b. HCO_3^- : 28 mEq/L
- T c. Phosphate : 4 mEq/L
- T d. PCO_2 : 45 mEq/L
- T e. SO_2^{--} : 1 mEq/L.

Q. 05. **Plasma concentration of ICF are as follows**
- T a. Cl^- : 4 mEq/L
- T b. HCO_3^- : 10 mEq/L
- T c. Phosphate : 75 mEq/L
- T d. PCO_2 : 46 mEq/L
- T e. SO_2^{--} : 2 mEq/L.

Q. 06. **Chemical composition of extracellar fluid are**
- T a. Cl^- : 108 mmol/Liter
- T b. protein : 2 mg/dL
- F c. Na^+ : 10 mmol/Liter
- F d. K^+ : 4 mmol/Liter
- F e. HCO_3^- : 10 mmol/Liter.

Q. 07. **Sodium ion concentration fall in plasma**
- T a. Reduces plasma osmolality
- T b. May result from xecessive production of ADH
- F c. Decreases intrcellular volume
- F d. Increases thirst
- F e. Increases the severity of oedema.

Q. 08. **Excessive sodium retension causes**
- T. a. Decrease renin production
- T b. Increase central venous presssure
- T c. Increase ADH secretion
- T d. Decrease aldosterone secretion
- F e. Loss of total body mass.

Q. 09. **Potasssium ion concentration in ECF**
- T a. Hyperkalaemia may cause cardiac arrest
- T b. Prolonged of Q-T interval occurs in hypokalaemia
- T c. It's uptake is increased by insulin
- F d. Aldosterone increase potassium reabsorption from the renal tubules
- F e. Potassium level in the ECF is decreased in acidosis.

Q. 10. **Chemical composition of intracellular fluid are**
- T a. Ca^{++} : 2.4 mmol/Liter
- T b. K^+ : 140 mmol/Liter
- T c. HCO_3^- : 24 mmol/Liter
- F d. Na^+ : 142 mmol/Liter
- F e. glucose : 0-20 mmol/Liter.

Q. 11. **Extra cellular fluid contains**
- T a. PO_2 : 35 mm of Hg
- T b. PCO_2 : 46 mm of Hg
- T c. Proteins : 2 gm%.
- F d. Na^+ : 145 mEq/dL
- F e. K^+ : 5 mEq/dL

Q. 12. **Intracellular fluid contains**
- T a. PO_2 : 20 mm of Hg
- T b. Na^+ : 10 mEq/L
- F c. K^+ : 125 mEq /L
- F d. PO_2 : 25 mm of Hg.
- F e. proteins : 10 gm%.

Q. 13. **Anion gap**
- T a. It is the difference between unmeasured anions and unmeasured cations

T b. Anion gap is increased in metabolic acidosis
T c. It is normally 10-18 mEq/L
T d. Anion gap detects the presence of acid-base disorder even in normal pH
F e. It is decreased in metabolic acidosis.

Q. 14. **Extracellular fluid**
T a. contains large amount of bicarbonate
T b. contains large amount of amino acid
T c. moves throughout the body
F d. contains large amount of potassium
F e. contains large amount of phosphate.

Q. 15. **Regarding osmotic presssure**
T a. It is the amount of pressure reqiured to prevent osmosis
T b. It is exerted by the nondiffusible solutes of the sodium
T c. Is decreased in hypoalbuminaemia
F d. Is directly proportionate to the mass of the solute
F e. Osmotic pressure of plasma is about 190 mosm/L.

Q. 16. **Regarding body fluid in a 70 kg adult male**
T a. Total body fluid is about 42 liters
T b. ICF is more than ECF
T c. Plasma volume is about 5% of the total body weight
T d. Total blood volume is about 8% of the total body weight
F e. Female has more body fluid than male due to excessive adipose tissue.

Q. 17. **Concerning body fluid**
T a. Interstitial fluid is an ultrafiltrate of plasma
T b. ECF has a greater osmotic strength than ICF.
T c. There is contineous loss of water via skin
F d. ECF has a higher H^+ concentration than ICF
F e. Plasma is an ICF.

Q. 18. **Features of alkalosis are**
T a. Tetany
T b. Overexcitation of nervous tissue
T c. Alkaline urine
F d. Hyperventilation
F e. Myocardial depression.

Q. 19. **Plasma**
T a. contain kallikrein.
T b. is the fluid portion of blood.
T c. is a remarkable solution containing ions.
F d. does not contain Hageman factor.
F e. is very much similar with serum.

Q. 20. **Plasma volume**
T a. helps to measure interstitial fluid volume.
T b. can be measured by ^{125}I-albumin
T c. can be measured by T-1824
F d. can be measured by ^{125}I-iothalamate
F e. can be measured by ^2H_2O

Q. 21. **Plasma volume can be measured by**
T a. direct method
T b. radioactive sodium
T c. radioactive iothalamate
F d. heavy water
F e. antipyrine.

Q. 22. **ECF volume is measured by**
T a. Renin-angiotensin-aldosterone system
T b. Vasopressin mechanism
T c. Thirst mechanism
T d. Epinephrine nor epinephrine mechanism
T e. Osmosodium receptor mechanism.

Q. 23. **D_2O is used to determine**
T a. Total body water
F b. ICF
F c. ECF
F d. Plasma volume
F e. All.

Q. 24. **Raised ECF K^+ levels seen in**
T a. Endolymph
F b. Ectolyrnph
F c. Aquous humour
F d. Vitreous humour
F e. All.

Q. 25. **In a man weighing 70kg, water content of body is :**
T a. 40-45 L
F b. 20-30 L
F c. 30-40 L
F d. 50-60 L
F e. 25-30 L.

Q. 26. **D_2O (Deuterium oxide) is used to measure volume of**
T a. Total body water
F b. Blood
F c. Extracellular fluid
F d. Intracellular fluid
F e. All.

Q. 27. **Regarding oedema**
T a. May be caused by malnutrition
T b. May be caused by increased vascular permeability
T c. Can be seen in liver disease
T d. Is caused by decreased plasma albumin concentration
T b. Means excess ECF volume.

Q. 28. **Body buffer**

T a. Acts by conversion of strong acid into weak acid
T b. They provide quick defense against acid-base disorder
F c. They can correct the acid-base disorder all the way back to normal
F d. Bicarbonate buffer is more powerfull than protein buffer
F e. They are mixture of weak acid and weak base.

Q. 29. **Regarding pH**

T a. pH is the negative logarithm of hydrgeon ion concentration to the base 10.
T b. pH of blood is directly proportionate to the PCO_2
T c. pH of urine is normally less than 7
F d. pH of arterial blood range from 7.2 to 7.6
F e. pH of blood is directly proportionate to the HCO_3^-

Q. 30. **The quantity of water lost as sweat per day is**

T a. 600 to 800 cc
F b. 100 to 200cc
F c. 1000 to 1200cc
F d. 300 to 400cc
F e. Above 1200 cc.

Q. 31. **A substance on I/V injection was found to be distributed through thirty percent of body water. It probably-**

T a. Did not enter cells of body
F b. Did not pass freely through blood capillaries
F c. Was distributed evently throughout body water
F d. Was excluded from CSF
F e. All.

13
Urinary System

Physiological Anatomy of the Kidneys

General organization of the kidneys and urinary tract : The two kidneys lie on the posterior wall of the abdomen, outside the peritoneal cavity. Each kidney of the adult human weights about 150 grams and is about the size of a *clenched fist*. The medial side of each kidney contains an inverted region called the *hilum* through which pass the renal artery and vein, lymphatics, nerve supply, and ureter that carries the final urine from the kidney to the bladder, where it is stored until emptied. If the kidney is disected from top to bottom, the two major regions that can be visualized are the outer cortex and the inner region referred to as the medulla. The medulla of the kidney is divided into multiple cone shaped masses of tissue called renal pyramids. The base of each pyramid originates at the border between the cortex and medulla and terminates in the papilla, which projects into the space of the renal pelvis, a funnel-shaped continuation of the uper end of the ureter. The outer border of the pelvis is divided into open ended pouches called *major calices* that extend downward and divide into *minor calices*, which collect urine from the tubules of each papilla. The walls of the calices, pelvis, and ureter contain contractile elements that propel the urine toward the bladder, where urine is stored until it is emptied by micturition.

(Ref. Guyton & Hall 11th edition, page 308, 309)

In the kidneys, a fluid that resembles plasma is filtered through the glomerular capillaries into the renal tubules (*glomerular filtration*). As this glomerular filtrate passes down the tubules, its volume is reduced and its composition altered by the processes of *tubular reabsorption* (removal of water and solutes from the tubular fluid) and *tubular secretion* (secretion of solutes into the tubular fluid) to form the urine that enters the renal pelvis. A comparison of the composition of the plasma and an average urine specimen illustrates the magnitude of some of these changes and emphasizes the manner in which wastes are eliminated while water and important electrolites and metabolites are conserved. Furthermore, the composition of the urine can be varied, and many homeostatic regulatory mechanisms minimize or prevent changes in the composition of the ECF by changing the amount of water and various specific solutes in the urine. From the renal pelvis, the urine passes to the bladder and is expelled to the exterior by the process of *urination or micturition*.

The kidneys are also endocrine organs, making *kinins and 1,25-dihydroxy-cholecalciferol* and making and secreting *renin*.

The component parts of the Urinary system

1. A pair of kidneys : Form urine.
2. A pair of ureters : Convey urine from kidney to bladder.
3. A urinary bladder : Temporary reserviour of urine.
4. Urethra : Excrete urine from bladder to the exterior.

Nephron

I. *Definition* : It is the structural and functional unit of the kidney.

II. *Parts* : It consists of two parts :
   a. Glomerulus.
   b. Renal tubules : *It consists of-*
      i. Bowman's capsule
      ii. Proximal convoluted tubule
      iii. Loop of Henle
         * Descending limb of the loop of Henle
         * Ascending limb of the loop of Henle
      iv. Distal convoluted tubule
      v. Collecting tubule.

(Ref. Ganong 22th edition, page 699)

III. *Total number of nephron* : Each kidney in the human contains about ***1 million nephrons***, each capable of forming urine. The kidney cannot regenerate new nephrons. Therefore, with renal injury, disease, or normal aging, there is a gradual decrease in nephron number. After age 40, the number of functioning nephrons usually decreases about 10 per cent every 10 years; thus, at age 80, many people have 40 per cent fewer functioning nephrons than they did at age 40. This loss is not life-threatening because adaptive changes in the remaining nephrons allow them to excrete the proper amounts of water, electrolytes, and waste products.

(Ref. Guyton & Hall 11th edition, page 310)

There are approximately 1.3 million nephrons in each human kidney.

(Ref. Ganong 22th edition, page 699)

IV. *Total length of the nephrons* : The total length of the nephrons, including the collecting ducts, ranges from 45 to 65 mm.

(Ref. Ganong 22th edition, page 702)

Parts of the Kidney

Kidney consist of two parts :

1. *Outer cortex :* Reddish colour due to the large blood supply.
2. *Inner medulla :* Pale in colour due to the less blood supply.

Content of the cortex :

i. Renal corpuscles
   a. Glomerulus
   b. Bowman's capsule.
ii. Proximal convoluted tubules (PCT).
iii. Distal convoluted tubules (DCT) .
iv. Collecting tubules (CT).
v. Afferent and efferent arterioles.
vi. Peritubular capillary plexus.
vii. Juxta glomerular apparatus.

Content of the medulla :

i. Loop of Henle.
   a. Thin decending limb of the loop of Henle.
   b. Thick ascending limb of the loop of Henle.
ii. Collecting tubule.
iii. Vasa recta.

(Ref. Ganong 22th edition & Guyton 11th edition)

Renal corpuscle

Renal (Malpigian) corpuscle, are small rounded masses composed of two parts glomerulas and Bowman's capsule.

i. *Glomerulus* : It is about 200 micrometer in diameter. It is formed by the invagination of a tuft of capillaries into the dilated blind end of the nephron (*Bowman's capsule*). The capillaries are supplied by an *afferent arteriole* and drained by slightly smaller *efferent arteriole*.
ii. *Bowman's capsule* : It is the initial dilated part of the renal tubule which contains an invaginated tuft of capillaries- *the glomerulus*.

Glomerular membrane : There are two cellular layers seperating the blood from the glomerular filtrate in Bowman's capsule :

a. *Endothelium of the glomerular capillaries* : The endothelium of the glomerular capillaries is fenestrated, with pores that are 70-90 nm in diameter.
b. *Epithelium of the Bowman's capsule* : The specialized epithelium of the Bowman's capsule that is made up of *podocytes* overlying the capillaries. The cells of the epithelium *(podocytes)* have numerous pseudopodia that interdigitate to form filtration slits along the capillary wall. The slits are approximately 25 nm wide, and each is closed by a thin membrane.
c. *Basal lamina* : The capillary endothelium and the epithelium of the Bowman's capsule are seperated by a basal lamina. The basal lamina does not contain visible gaps or pores. Stellate cells called *mesangial cells* are located between the basal lamina and the endothelium. Mesangial cells are contractile and play a role in the regulation of glomerular filtration. They also secrects various substances, take up immune complexes, and are involved in the production of glomerular disease.

Function of the glomerular membrane : Functionally the glomerular membrane permits the free passage of neutral substances up to 4 nm in diameter and almost totally excludes those with diameters greater than 8 nm. However, the charges on molecules as well as their diameters affect their passage into Bowman's capsule. The total area of glomerular capillary endothelium across which filtration occurs in humans is about 0.8 m^2.

(Ref. Ganong 22th edition, page 699, 700)

Q. **Why proteins cannot pass through the glomerular membrane?**

Ans. The pores of the membrane are larger (80 Å or 8 nanometer) than the molecular diameter of the plasma protein-albumin (6 nanometer), yet the protein can not pass through the membrane. Because the glomerular pores are lined with a complex of glycosylated proteins that have very strong negative electrical charges. The plasma proteins also have strong negative electrical charges. Therefore, electrostatic repulsion of the protein molecules by the pores walls keeps these molecules from passing through.

(Ref. Guyton & Hall 11th Edition; Page 317)

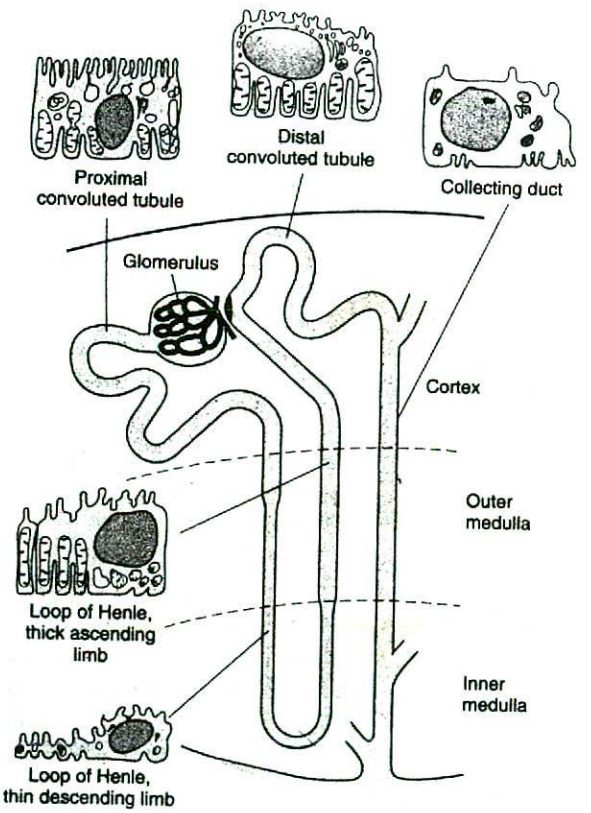


Fig. 13-1. Diagram of a juxtamedullary nephrone. The main histologic features of the cells that make up each prtion of the tubule are also shown.

Proximal convoluted tubule

The human *proximal convoluted tubule* is about 15 micro meter long and 55 micro meter in diameter. Its wall is made up of a single layer of cells that interdigitate with one another and are united by apical tight junctions. Between the bases of the cells, there are extensions of the extracellular space called the *lateral intercellular spaces*. The luminal edges of the cells have a striate *brush border* due to the presence of innumerable 1 x 0.7 micro meter microvilli.

The *convoluted portion of the proxial tubule* (pars convoluta) drains into the straight portion (pars recta), which forms the first part of the loop of Henle.

(Ref. Ganong 22th edition, page 700)

Loops of Henle

The nephrons with glomeruli in the outer portions of the renal cortex have short loops of Henle (*cortical nephrons*), whereas those with glomeruli in the juxtamedullary region of the cortex (juxtamedullary nephrons) have long loops extending down into the medullary pyramids. In humans, only 15% of the nephrons have long loops.

i. *Thin segment of the decending limb of the loop of Henle* : It has an epithelium made up of attenuated, flat cells. The total length of the thin segment of the loop varies from 2 to 14 mm. It ends in the thick segment of the asceding limb.

ii. *Thick segment of the asceding limb of the loop of Henle* : It is about 12 mm in length. The cells of the *thick ascending limb* are cuboid. They have numerous mitochondria, and the basilar portions of their cell membranes are extensively invaginated.

The thick ascending limb of the loop of Henle reaches the glomerulus of the nephron from which the tubule arose and passes close to its afferent arteriole and efferent arteriole. The

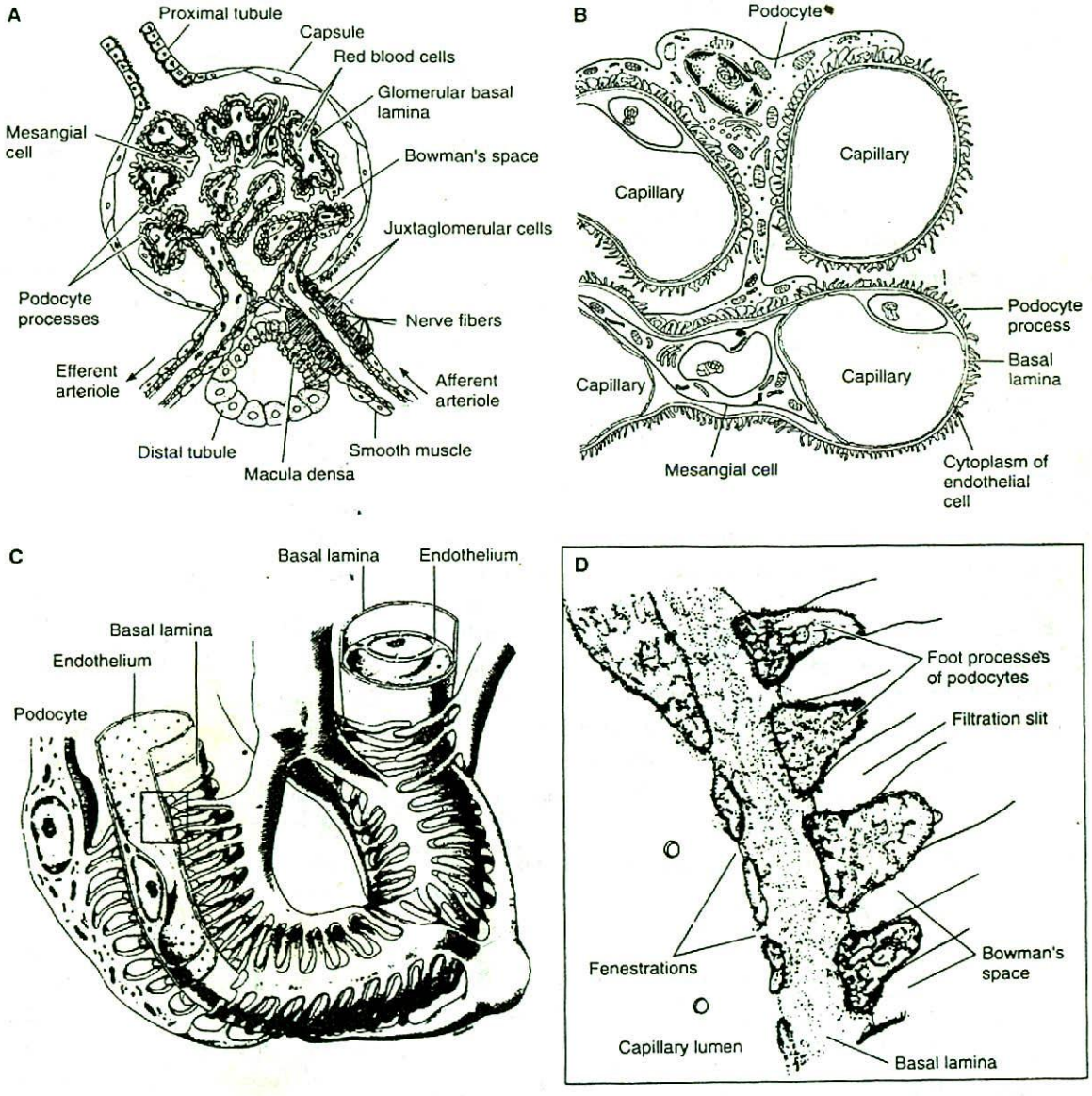


Fig. 13-2. Stuctural details of glomerulus. A: Section through vascular pole, showing capillary loops. B: Relation of mesangial cells and podocytes to glomerular capillaries. C: Detail of the way podocytes form filtration slits on the basal lamina, and the relation of the lamina to the capillary endothelium. D: Enlargement of the rectangle in C to show the podocyte processes.

walls of the afferent arterioles contain the *renin-secreting* juxtaglomerular cells. At this point, the tubular epithe- lium is modified histologically to form the *macula densa*. The juxtaglomerular cells and the macula densa, and the lacis cells near them are known collectively as the *juxtaglomerular apparatus.*

(Ref. Ganong 22th edition, page-700)

Distal convoluted tubule : The *distal convoluted tubule* is about 5 mm long. Its epithelium is lower than that of the proximal tubule, and although there are a few microvilli, there is no distinct brush border.

(Ref. Ganong 22th edition, page-700)

Collecting ducts : The distal tubules coalesce to form *collecting ducts* that are about 20 mm long and pass through the renal cortex and medulla to empty into the pelvis of the kidney at the apexes of the medullary pyramids. The epithelium of the collecting ducts is made up of-

i. *Principal cells (Pcells)* : The P cells, which predominate, are relatively tall and have few organelles.

Function : They are involved in Na^+ reabsorption and vasopressin stimulated water reabsorption.

ii. *Intercalated cells (I cells)* : The I cells, which are present in smaller numbers and are also found in the distal tubules, have more microvilli, cytoplasmic vesicles, and mitochondria.

Function : They are concerned with acid secretion and HCo_3^- transport.

(Ref. Ganong 22th edition, page-700)

N.B.

Cells in the kidneys that appear to have a secretory function include not only the juxtaglomerular cells but also some of the cells in the interstitial tissue of the medulla. These cells are called ***type I medullary interstitial cells***. They contain lipid droplets and probably secrete prostaglandins, predominantly PGE_2. PGE_2 is also secreted by the cells in the collecting ducts, and prostacyclin (PGI_2) , as well as other prostaglandins are secreted by the arterioles and glomeruli.

(Ref. Ganong 22th edition, page-702)

Agents causing contraction or relaxation of mesangial cells

Contraction	*Relaxation*
Endothelins	ANP
Angiotensin II	Dopamin
Vasopressin	PGE_2
Norepinephrine	cAMP
Platelet activating factor	
Platelet derived growth factor	
Thromboxane A_2	
PGE_2	
Leukotriens C_4 and D_4	
Histamine.	

Multiple function of the kidneys in homeostasis

Most people are familiar with one important function of the kidneys- to rid the body of waste materials that are either ingested or produced by metabolism. A second function that is especially critical is to control the volume and composition of the body fluids. For water and virtually all electrolytes in the body, balance between intake (due to ingestion or metabolic production) and output (due to excretion or metabolic consumption) is maintained in large part by the kidneys. This regulatory function of the kidneys maintains the stable environment of the cells necessary for them to perform their various activities.

The kidneys perform their most important functions by filtering the plasma and removing substances from the filtrate at variable rates, depending on the needs of the body. Ultimately, the kidneys "clear" unwanted substances from the filtrate (and therefore from the blood) by excreting them in the urine while returning substances that are needed back to the blood.

Kidneys serve multiple functions, including the following

1. Excretion of metabolic waste products and foreign chemicals.
2. Regulation of water and electrolyte balances.
3. Regulation of body fluid osmolality and electrolyte concentrations.
4. Regulation of acid-base balance.
5. Regulation of arterial pressure.
6. Secretion, metabolism, and excretion of hormones
7. Gluconeogenesis.

(Ref. Guyton & Hall 11th Edition, Page 307)

Description of the kidney functions :

i. *Excretion of metabolic waste products, foreign chemicals, drugs, and hormone metabolites* : The kidneys are the primary means for eliminating waste products of metabolism that are no longer needed by the body. These products include *urea* (from the metabolism of amino acids), *creatinine* (from muscle creatine), *uric acid* (from nucleic acids), the end products of hemoglobin breakdown (such as *bilirubin*), and metaholites of various *hormones*. These waste products must be eliminated from the body as rapidly as they are produced. The kidneys also eliminate most *toxins* and other foreign substances that are either produced by the body or ingested, such as *pesticides, drugs, and food additives.*

ii. *Regulation of water and electrolyte balances* : For maintenance of homeostasis, excretion of water and electrolytes must precisely match intake. If intake exceeds excretion, the amount of that substance in the body will increase. If intake is less than excretion, the amount of that substance in the body will decrease.

Intakes of water and many electrolytes usually are governed mainly by a person's eating and drinking habits, necessitating that the kidneys adjust their excretion rates to match intakes of the various substances.

Response of the kidneys to a sudden 10-fold increase in

sodium intake from a low level of 30 mEq/day to a high level of 300 mEq/day is that within 2 to 3 days after raising sodium intake, renal excretion also increases to about 300 mEq/day, so that a balance between intake and output is re-established. However, during the 2 to 3 days of renal adaptation to the high sodium intake, there is a modest accumulation of sodium that raises extracellular fluid volume slightly and triggers hormonal changes and other compensatory responses that signal the kidneys to increase their sodium excretion.

The capacity of the kidneys to alter sodium excretion in response to changes in sodium intake is enormous. Experimental studies have shown that in many people, sodium intake can be increased to 1500 mEq/day (more than 10 times normal) or decreased to 10 mEq/day (less than 1/10 normal) with relatively small changes in extracellular fluid volume or plasma sodium concentration. This is also true for water and for most other electrolytes, such as chloride, potassium, calcium, hydrogen, magnesium, and phosphate ions.

iii. *Regulation of arterial pressure* : Kidneys play a dominant role in long-term regulation of arterial pressure by excreting variable amounts of sodium and water. In addition, the kidneys contribute to short-term arterial pressure regulation by secreting vasoactive factors or substances, such as renin, that lead to formation of vasoaetive products (for example, angiotensin II).

iv. *Regulation of acid-base balance* : The kidneys contribute to acid-base regulation, along with the lungs and body fluid buffers, by excreting acids and by regulating the body fluid buffer stores. The kidneys are the only means for eliminating from the body certain types of acids generated by metabolism of proteins, such as sulfuric acid and phosphoric acid.

v. *Regulation of erythrocyte production* : The kidneys secrete erythropoietin, which stimulates the production of red blood cells. One important stimulus for erythropoietin secretion by the kidneys is hypoxia. In the normal person, the kidneys account for almost all the erythropoietin secreted into the circulation. In people with severe kidney disease or who have had their kidneys removed and have been placed on hemodialysis, severe anemia result of decreased erythropoietin production.

vi. *Regulation of 1,25-dihydroxy vitamin D_3 production* : The kidneys produce the active form of vitamin D, 1 ,25-dihydroxy vitamin D_3 (*calcitriol*) by hydroxylating this vitamin at the number '1' position. Calcitriol is essential for normal calcium deposition in bone and calcium reabsorption by the gastrointestinal tract.

vii. *Glucose synthesis* : The kidneys synthesize glucose from amino acids and other precursors during prolonged fasting, a process referred to as *gluconeogenesis*. The kidneys' capacity to add glucose to the blood during prolonged periods of fasting rivals that of the liver.

(Ref. Guyton & Hall 11th Edition, Page 307, 308)

With chronic kidney disease or acute failure of the the kidneys, these homeostatic functions are disrupted, and severe abnormalities of body fluid volumes and composition rapidly occur. With complete renal failure, enough accumulation in the body of potassium, acids, fluid and other substances occurs within a few days to cause death, unless clinical interventions such as hemodialysis are initiated to restore, at least partially, the body fluid and electrolyte balances.

(Ref. Guyton & Hall 11th Edition, Page-280)

Hormones of the kidneys

The kidneys produce three hormones :

1. *1,25-dihydroxycholecalciferol* : It increases the absorption of ca^{++}.
2. *Renin* : It Converts angiotensinogen into angiotensinogen-I. Angiotensinogen-I then converted into angiotensinogen-II which increases the systolic and diastolic blood pressure by vasoconstriction.
3. *Erythropoietin* : It increases the synthesis of haemoglobin, and production and release of red blood cells from the bone marrow- during hypoxia or anaemia.

Hormones that act on kidneys

Hormones that act on the kidneys are :

i. Vasopressin or anti-diuretic hormone-ADH
ii. Aldosterone
iii. Parathyroid hormone
iv. Catcitonin
v. Atrial natriuretic peptide-ANP

Vasopressin : Antidiuretic hormone (ADH) or vasopressin is secreted from the posterior pituitary gland due to osmotic stimuli i.e. hyperosmolarity and non-osmotic stimuli i.e hypovolaemia.

i. *Major site of action of ADH* : is the V_2-receptor in the basolateral membrane of the cells of distal tubule, collecting tubule and collecting duct.
ii. *Function* :
   a. Increase H_2O reabsorption from distal tubule, collecting tubule and collecting duct by increasing permeability to H_2O.
   b. Decrease in renal medullary blood flow.

Aldosterone : Aldosterone is a steroid hormone, secreted from the Zona glomerulosa of the adrenal cortex. Renin-angiotensin system regulates aldosterone secretion in addition to hyponatraemia, hyperkalaemia and excessive ACTH.

Physiological effects on renal tubules are :

i. Primary action : Conservation of Na^+ from distal tubule, collecting tubule and collecting ducts by

stimulation of the Na^+-K^+ / Na^+-H^+ cation exchange process.

ii. Secondary effects : Secretion of K^+ and H^+ into the tubules.

iii. On GFR : It has no direct effect on GFR, renal plasma flow or renin production. By stimulating Na reabsorption aldosterone causes passive water retention and the resulting expansion of ECF volume. Then leads to an increase in GFR and renal blood flow and a decrease in renin production.

Parathyroid hormone : It is secreted by the four parathyroid glands. It level rises as serum calcium falls.

Physiological effects on renal tubules are :

i. Increased tubular reabsorption of calcium

ii. Increased excretion of phosphate (by inhibiting reabsorption).

Calcitonin : Calcitonin is produced by thyroid C-cells.

Physiological effects on renal tubules are :

i. Increased excretion of calcium and phosphate

ii. Inhibits renal 1 alpha-hydroxylase activity, which leads to a decrease in the synthesis of calcitriole.

Atrial natriuretic peptide-ANP : ANP is released from atrial cardiocytes. It exerts a hormonal influence on kidneys, which results in changes in intrarenal hemodynamics.

Physiological effects on renal tubules are :

i. Increases GFR

ii. Dilatation of the afferent arterioles

iii. Natriuresis i.e increased urinary Na^+ excretion

iv. Inhibition of renin secretion.

Renal blood supply

Blood flow to the two kidneys is normally about 22 per cent of the cardiac output, or 1100 ml/minute. The ***renal artery*** enters the kidney through the hilum and then branches progressively to form the *interlobar arteries*, *arcuate arteries*, *interlobular arteries* (also called radial arteries), and *afferent arterioles*, which lead to the glomerular capillaries, where large amounts of fluid and solutes (except the plasma proteins) are filtered to begin urine formation. The distal ends of the capillaries of each glomerulus coalesce to form the *efferent arteriole*, which leads to a second capillary network, the *perituhular capillaries*, that surrounds the renal tubules.

The renal circulation is unique in that it has two capillary beds, the *glomerular and peritubular capillaries*, which are arranged in series and separated by the efferent arterioles that help to regulate the hydrostatic pressures in both sets of capillaries. High hydrostatic pressure in the glomerular capillaries (about *60 mm of Hg*) causes rapid fluid filtration, whereas a much lower hydrostatic pressure in the peritubular capillaries (about *13 mm Hg*) permits rapid *fluid reabsorption*. By adjusting the resistances of the afferent and efferent arterioles, the kidneys can regulate the hydrostatic pressures in both the glomerular and the peritubular capillaries, thereby changing the rate of glomerular filtration and/or tubular reabsorption in response to body homeostatic demands.

The peritubular capillaries empty into the vessels of the venous system, which run parallel to the arteriolar vessels and progressively form the *interlobular vein, arcuate vein, interlobar vein, and renal vein*, which leaves the kidney beside the renal artery and ureter.

(Ref. Guyton & Hall 11th edition, page 309)

Blood flow to the two kidneys is about 1.2 - 1.3 L/minute or just under 25% of the cardiac output.

(Ref. Ganong 22th edition, page-702)

Autoregulation of renal blood flow : The process by which the renal blood flow remain near the normal level despite considerable change in the arterial pressure, is called autoregulation of renal blood flow.

(Ref. Guyton & Hall 11th edition, page 323)

Mechanism of autoregulation of renal blood flow : The renal blood flow is autoregulated by the following ways :

a. Afferent arteriolar vasodilator feed back mechanism : Please see autoregulation of GFR.

b. Myogenic mechanism : When arterial pressure rises, it stretches the wall of the ateriole, this inturn causes secondary contraction of arteriole and decreases renal blood flow back toward normal.

(Ref. Guyton & Hall 11th edition, page 325)

Peculiarities of the renal circulation

a. ***Anatomical peculiarities of the renal artery*** :

i. After only a relatively few branching of the renal artery, the glomerular capillaries are formed. The efferent arteriole from the glomerulus is narrower than the afferent. For these reasons, the capillary blood pressure in the renal glomerulus is rather high, about 45 or 60 mm Hg. This high blood pressure in the glomerular capillaries facilitates the filtration.

ii. The efferent arteriole from the glomerulus however offers considerable resistance to the flow of blood and, as a result, the blood pressure falls beyond the efferent arteriole. In the peritubular capillary, it is only 13 or 8 mm Hg or so. This facilitates reabsorption from the tubules.

iii. In the vasa recta, velocity of circulation is very slow. This helps to preserve the medullary gradient.

iv. The direction of the flow of blood in the vasa recta and its U shaped loop, also help to preserve the medullary gradient and conservation of water by the kindey.

v. Mesangial cells can control the diameter of the glomerular capillaries and thus the GFR.

b. ***Functional specialities of the renal artery*** :

i. The renal blood (or plasma) flow is very high, plasma flow being about 650 ml/min.

ii. Renal vessels are constricted by the traditional agents : sympathetic stimulation, adrenaline or noradrenalin administration. Angiotensin II stimulates mainly the afferent arterioles to the glomerulus. Fever, due to most causes, causes renal vasodilatation. Anoxia causes renal vasoconstriction.

iii. Autoregulation of renal blood flow is remarkable. Between say (80-180) mm of Hg of systemic blood pressure, the glomerular flow is not affected.

Difference between glomerular and peritubular capillary

Glomerular capillary	*Peritubular capillary*
i. It opens in the efferent arteriole (Arterial end).	i. It opens in the venules (Venous end).
ii. It is high pressure capillary bed (60 or 45 mm of Hg).	ii. It is low pressure capillary bed (13 or 8 mm of Hg).
iii. Here filtration occurs.	iii. Here reabsorption occurs.
iv. It receives blood from afferent arteriole.	iv. It receives blood from efferent arteriole.
v. It remains invaginated inside the Bowman's capsule.	v. It remains outside the Bowman's capsule & arranged around the PCT, DCT & CT.

Blood pressure in renal vessels

Vessels	*Pressure in vessels (mm of Hg)*	
	Beginning	*End*
1. *Renal artery*	*100*	*100*
2. *Interlobar, arcuate and interlobular arteries*	*100*	*85*
3. Afferent arteriole	85	60
4. Glomerular capillaries	60	59
5. *Efferent arteriole*	*59*	*18*
6. *Peritubular capillaries*	*18*	*08*
7. Interlobar, arcuate and interlobular vein	08	04
8. *Renal vein*	*04*	*~ 04*

(Ref. Guyton. & Hall 11th edition, page 321)

Pressure in the renal tubules

1. Bowman's capsule : 18 mm of Hg
2. Proximal convoluted tubules : 18 mm of Hg
3. Distal convoluted tubules : 10 mm of Hg
4. Colltecting tubules : 02 mm of Hg
5. Renal pelvis : 00 mm of Hg
6. Interstitial fluid : 06 mm of Hg.

(Ref. Guyton & Hall 11th edition).

Glomerular filtration (GF)

Definition : The filtration that occurs through the glomerular capillary is called glomerular filtration.

Causes (Dynamics) of glomerular filtration : Due to the effective filtration pressure glomerular filtration (GF) occurs. The pressure inside the glomerular capillaries promotes glomerular filtration. On the other hand colloidal osmotic pressure in blood and the pressure in the Bowman's capsule opposes the filtration.

1. *Factors favouring filtration (mm of Hg)* :
   a. Glomerular hydrostaticy pressure : 60
   b. Bowman's capsule colloid osmotic pressure : 0
2. *Factors opposing filtration (mm of Hg)* :
   a. Bowman's capsule hydrostatic pressur : 18
   b. Glomerular capillary colloidal osmotic pressure : 32

So net filtration pressure = 60 - (18 + 32) mm of Hg
= + 10 mm of Hg.

So net filtration pressure +10 mm of Hg causes the filtration of glomerular filtrate.

(Ref. Guyton & Hall 11th edition, page 318)

Glomerular filtrate

The fluid that filters through the glomerulus into Bowman's capsule is called glomerular filtrate.

Normal glomerular filtrate = 180 liter/day.
= 7.5 liter/hour
= 125 ml/minute

P^H of glomerular filtrate = 7.4

(Ref. Ganong 22th edition, page 706)

Composition of glomerular filtrate (character) :

Its composition is as the fluid that filters from the arterial ends of the capillaries into the interstitial fluid.

1. It is isotonic to plasma (osmotic pressure- 300 mosm/liter).
2. It is devoid of cellular elements, including red blood cells.
3. It is essentially protein free, may contains about 0.03% protein, or about 1/240, the protein in the plasma.

4. The electrolyte and other solute composition is similar to that of plasma. But-
   a. The concentration of the nonprotein negative ions (Cl^-, HCO_3- etc) are 5% higher than plasma.
   b. The concentration of positive ions are about 5% lower than plasma.
   c. Almost one half of the plasma calcium and most of the fatty acids are bound to proteins, and these bound proteins are not filtered through the glomerular capillaries.

Summary : Glomerular filtrate is the same as the plasma except that it has no significant amount of protein.

(Ref. Guyton & Hall-11th Edition and others)

Difference between glomerular filtrate & Urine

Glomerular filtrate	*Urine*
1. It is alkaline pH- 7.4.	1. It is always acidic pH - 5.5-6.5.
2. It is isotonic to plasma (300 mosm/l).	2. It is hypertonic to plasma.
3. It is about 180 liters /day.	3. It is about 1.2-1.5 liters/ day.
4. Glomerular filtration rate-125ml/min.	4. Urine formation rate - 1ml/min.
5. It's composition is near ly similar to plasma.	5. It is not similar to plasma.

Glomerular Filtration Rate (GFR)

Definition : The quantity of glomerular filtrate formed in each minute by all the nephrones of both kidneys is called glomerular filtration rate (GFR).

Normal values : The GFR in an average-sized normal man is approximately 125 ml/minute.

i. Its magnitude correlates fairly well with surface area, but values in women are 10% lower than those in men even after correction for surface area.

ii. A rate of 125 ml/minute is 7.5 litres/hour or 180 litres/day, where as the normal urine volume is about 1 L/day.

iii. Thus, 99% or more of the filtrate is normally reabsorbed.

iv. At the rate of 125 mL/minute, the kidneys filter in 1 day an amount of fluid equal to 4 times the total body water, 15 times the ECF volume, and 60 times the plasma volume.

(Ref. Ganong 22th edition, page-706)

Control of GFR

The factors governing filtration across the glomerular capillaries are the same as those governing filtration across all other capillaries, ie, the size of the capillary bed, the permeability of the capillaries, and the hydrostatic and osmotic pressure gradients across the capillary wall. For each nephron :

$$GFR = K_f [(P_{GC} - P_T) - (\pi_{GC} - \pi_T)]$$

1. K_f, the glomerular ultrafiltration coefficient, is the product of the glomerular capillary wall hydraulic conductivity (ie. its permeability) and the effective filtration surface area.
2. P_{GC} is the mean hydrostatic pressure in the glomerular capillaries.
3. P_T the mean hydrostatic pressure in the tubule.
4. π_{GC} the osmotic pressure of the plasma in the glomerular capillaries
5. π_T the osmotic pressure of the filtrate in the tubule.

(Ref. Ganong 22th edition, page 706)

Factors affecting the GFR

1. Changes in renal blood flow
2. Changes in glomerular capillary hydrostatic pressure
   i. Changes in systemic blood pressure
   ii. Afferent or efferent arteriolar constriction
3. Changes in hydrostatic pressure in Bowman's capsule
   i. Ureteral obstruction
   ii. Edema of kidney inside tight renal capsule
4. Changes in concentration of plasma proteins : dehydration, hypoproteinemia etc (minor factors)
5. Changes in K_f.
   i. Changes in glomerular capillary permeability
   ii. Changes in effective filtration surface area.

(Ref. Ganong 22th edition)

Renal fraction

The portion of the total cardiac output that passes through the kidneys is called the renal fraction.

i. The total cardiac output of 70 kg adult : 5600 ml/min.
ii. Rate of blood flow through both kidneys : 1200 ml/minute.

$$\text{So, Renal fraction} = \frac{1200 \times 100}{5600}$$

$$= 21\%$$

Range : 12-30 %.

(Ref. Guyton & Hall 11th Edition)

Filtration fraction

Filtration fraction is the ratio of the GFR to the renal plasma flow (RPF).

The normal plasma flow through both kindey = 650 ml/ minute.

The glomerular filtration rate = 125 ml/ min.

So, Filtration fraction $= \frac{125}{650}$

$= 0.19$

(Ref. Ganong 22th edition, page-708; Guyton 11th, Page-346)

Filtration Pressure

The filtration pressure is the net pressure forcing fluid through the glomerular membrane. It is about 10 mm Hg.

Filtration pressure is equal to the sum of glomerular hydrostatic pressure plus Bowman's capsule colloid osmotic pressure minus the sum of glomerular capillary colloidal osmotic pressure and Bowman's capsule hydrostatic pressure, that is -

i. *Factors favouring filtration (mm of Hg)* :
   a. Glomerular hydrostaticy pressure : 60
   b. Bowman's capsule colloid osmotic pressure : 0

ii. *Factors favouring filtration (mm of Hg)* :
   a. Bowman's capsule hydrostatic pressure : 18
   b. Glomerular capillary colloidal osmotic pressure : 32

So net filtration pressure = 60 - (18 + 32) mm of Hg
= + 10 mm of mg.

So net filtration pressure +10 mm of mg causes the filtration of glomerular filtrate.

(Ref. Guyton & Hall 11th edition)

Filtration co-efficient

K_f, the glomerular ultrafiltration coelficient, is the product of the glomerular capillary wall hydraulic conductivity (ie. its permeability) and the effective filtration surface area.

(Ref. Ganong 22th edition, page-706)

The K_f is a measure of the product of the hydraulic conductivity and surface area of the glomerular capillanes. The K_f cannot be measured directly, but it is estimated experimentally by dividing the rate of glomerular filtration by net filtration pressure :

$$K_f = \frac{GFR}{\text{Effective filtration pressure}}$$

$$= \frac{125}{10}$$

$= 12.5$ ml/min./mm of Hg of filtration pressure.

Because total GFR for both kidneys is about 125 ml/min and the net filtration pressure is 10 mm Hg, the normal K_f is calculated to be about 12.5 ml/min/mm Hg of filtration pressure.

When K_f is expressed per 100 grams of kidney weight, it averages about 4.2 ml/min/mm Hg per 100 grams of kidney weight, a value about 400 times as high as the K_f of most other capillary systems of the body; the average K_f of the other tissues in the body is only about 0.01 ml/min/mm Hg per 100 grams. This high K_f for the glomerular capillaries contributes tremendously to their rapid rate of fluid filtration.

Although increased K_f raises GFR, and decreased K_f reduces GFR, changes in K_f probably do not provide a primary mechanism for the normal day-to-day regulation of GFR. Some diseases, however, lower K_f by reducing the number of functional glomerular capillaries (thereby reducing the surface area for filtration) or by increasing the thickness of the glomerular capillary membrane and reducing its hydraulic conductivity. For example, chronic, uncontrolled hypertension and diabetes mellitus gradually reduce K_f by increasing the thickness of the glomerular capillary baesment membrane and, eventually, by damaging the capillaries so severely that there is loss of capillary function.

(Ref. Guyton & Hall 11th Edition, Page 318)

Autoregulation of GFR and renal blood flow

Feedback mechanisms intrinsic to the kidneys normally keep the renal blood flow and GFR relatively constant, despite marked changes in arterial blood pressure. These mechanisms still function in blood-perfused kidneys that have been removed from the body, independent of systemic influences. This relative constancy of GFR and renal blood flow is referred to as *autoregulation.*

The primary function of blood flow autoregulation in most other tissues besides the kidneys is to maintain delivery of oxygen and nutrients to the tissues at a normal level and to remove the waste products of metabolism, despite changes in the arterial pressure. In the kidneys, the normal blood flow is much higher than required for these functions. The major function of auto-regulation in the kidneys is to maintain a relatively constant GFR and to allow precise control of renal excretion of water and solutes.

The GFR normally remains autoregulated (that is, remains relatively constant), despite considerable arterial pressure fluctuations that occur during a person's usual activities. For instance, a decrease in arterial pressure to as low as 75 mm Hg or an increase to as high as 160 mm Hg changes GFR only a few percentage points. In general renal blood flow is autoregulated in parallel with GFR, but GFR is more efficiently autoregulated under certain conditions.

Importance of GFR autoregulation in preventing extreme changes in renal excretion : The autoregulatory mechanisms of the kidney are not 100 per cent perfect, but they do prevent potentially large changes in GFR and renal excretion of water and solutes that would otherwise occur with changes in blood pressure. One can understand the quantitative importance of autoregulation by considering the relative magnitudes of glomerular filtration, tubular reabsorption, and renal excretion and the changes in renal excretion that would occur without autoregulatory mechanisms.

Normally, GFR is about 180 L/day and tubular reabsorption is 178.5 L/day, leaving 1.5 L/day of fluid to be excreted in the urine. In the absence of autoregulation, a relatively small increase in blood pressure (from 100 to 125 mm Hg) would cause a similar 25 per cent increase in GFR (from about 180 to 225 L/day). If tubular reabsorption remained constant at 178.5 L/day, this would increase the urine flow to 46.5 L/day (the difference between GFR and tubular reabsorption), making a total increase in urine of more than 30-fold! Because the total plasma volume is only about 3 liters, such a change would quickly deplete the blood volume.

Mechenism of autoregulation of GFR and renal blood flow : But in reality, such a change in arterial pressure exerts much less of an effect on urine volume for two reasons :

1. Renal autoregulation prevents large changes in GFR that would otherwise occur and
2. There are additional adaptive mechanisms in the renal tubules that allow them to increase their reabsorption rate when GFR rises, a phenomenon referred to as *glomerulotubular balance.*
3. Yet, even with these special control mechanisms, changes in arterial pressure still have significant effects on renal excretion of water and sodium; this is referred to as *pressure diuresis or pressure natriuresis*, and it is crucial in regulation of body fluid volumes and arterial pressure.

(For details Please see Guyton 10th Edition, Page 290)

(Ref. Guyton & Hall 11th Edition, Page 323)

Juxta glomerular complex

The epithelial cells of the distal tubule that come in contact with the atrerioles (afferent and efferent) are more dense than the other tubular cells and are collectively called the macula densa. The macula densa cells appear to secrete some substance toward the arteriole. The smooth muscle cells of both the afferent and efferent arteriole are swollen and contain dark granules where they come in contact with macula densa. These cells are called *juxtaglomerular cells (JG)* and the granules are composed mainly of inactive renin. The whole complex of macula densa and juxta glomerular cells is called the *juxtaglomerular complex or juxtaglomerular apparatus*. The *juxtaglomerular* cells of this complex secrete renin which regulate blood pressure *(fig. 13.2).*

(Ref. Guyton & Hall 11th Edition)

Urinary and plasma concentrations of some physiologically important substances : *(Ref. Ganong 22th edition, page 699)*

	Concentration in		
Substance	*Urine (U)*	*Plasma (P)*	*U/P Ratio*
Glucose((mg/dL)	0	100	0
Na^+ (meq/L)	*90*	*140*	*0.6*
Urea (mg/dl)	900	15	60
Creatinine(mg/dl)	*150*	*1*	*150*

Plasma clearance or renal clearance

Definition : The rates at which different substances are "cleared" from the plasma provide a useful way of quantitating the effectiveness with which the kidneys excrete various substances. By definition, *the renal clearance of a substance is the volume of plasma that is completely cleared of the substance by the kidneys per unit time.* This concept is somewhat abstract because there is no single volume of plasma that is completely cleared of a substance.

Clearance principle : To illustrate the clearance principle, consider the following example : If the plasma passing through the kidneys contains 1 milligram of a substance in each milliliter and 1 milligram of this substance is also excreted into the urine each minute, then 1 ml/min of the plasma is 'cleared" of the substance. Thus, clearance refers to the volume of plasma that would be necessary to supply the amount of substance excreted in the urine per unit time. Stated mathematically,

$$C_s \times P_s = U_s \times V$$

Where C_s is the clearance rate of a substance s, P_s is the plasma concentration of the substance, U_s is the urine concentration of that substance, and V is the urine flow rate.

Plasma clearance of any substance can be determined by the following formula :

$$C_s = \frac{U_s \times V}{P_s}$$

Calculation : Thus, renal clearance of a substance is calculated from the urinary excretion rate (U_s x V) of that substance divided by its plasma concentration.

Plasma clearance =

Conc. of substance in urine x Volume of urine (ml/minute)
Concentration of substance in plasma in ml.

$$C_s = \frac{U_s \times V}{P_s}$$

Use of plasma clearance : However, renal clearance provides a useful way of quantifying the excretory function of the kidneys and can be used to quantify the rate at which blood flows through the kidneys as well as the basic functions of the kidneys : glomerular filtration, tubular reabsorption, and tubular secretion.

(Ref. Guyton & Hall 11th Edition, Page 343, 344)

Plasma clearance value of Urea is 70 ml - *Explain*

We know that the plasma clearance of any substance-

$$= \frac{\text{Conc. of substance in urine x Volume of urine (ml/min.)}}{\text{Concentration of substance in plasma in ml.}}$$

Normal concentration of urea in plasma = 0.26 mg/ml.

Amount of urea excreted in urine =18.2 mg/minute.

$$\text{Plasma clearance of Urea} = \frac{18.2 \times 1}{0.26}$$

$$= 70 \text{ ml.}$$

So, the clearance value of urea is 70 ml/min means-70 ml of plasma contain the amount of urea which is excreted in the urine per minute.

Determination of GFR from plasma clearance *(Inulin clearance)* : If a substance is freely filtered (filtered as freely as water) and is not reabsorbed or secreted by the renal tubules, then the rate at which that substance is excreted in the urine (U_s X V) is eqal to the filtration rate of the substance by the kidneys (GFR x P_s).

Thus,

GFR x Ps = Us x V

The GFR, therefore, can be calculated as the clearance of the substance as follows :

$$GFR = \frac{U_s \times V}{P_s}$$

$$= C_s$$

A substsnce that fits these criteria is inulin, a polysaccharide molecule with a molecular weight of about 5200. Inulin, which is not produced in the body, is found in the roots of certain plants and must be administered intravenously to a patient to measure GFR.

The plasma concentration of inulin is 1 mg/ml, urine concentration is 125 mg/ml, and urine flow rate is 1 ml/min. Therefore, 125 mg/min of inulin passes into the urine. Then, inulin clearance is calculated as the urine excretion rate of inulin divided by the plasma concentration, which yields a value of 125 ml/minute. Thus, 125 milliliters of plasma flowing through the kidneys must be filtered to deliver the inulin that appears in the urine. So, GFR is 125 ml/minute.

(Ref. Guyton & Hall 11th Edition, Page-344)

N.B.

Inulin is not the only substance that can be used for determining GFR. Other substances that have been used clinically to estimate GFR include *creatinine* and *radioactivc iothalamate*. Because creatinine is a by-product of skeletal muscle metabolism, it is present in the plasma at a relatively constant concentration and does not require intravenous infusion into the patient. For this reason, creatininc clearance is perhaps the most widely used method of estimating GFR clinically. However, creatinine is not a perfect marker for GFR because a small amount of it is secreted by the tubules, so that the amount of creatinine excreted in the urine slightly exceeds the amount filtered. There is normally a slight error in measuring plasma creatinine that leads to an overestimate of the plasma concentration and fortuitously, these two errors tend to cancel each other. Therefore, the clearance of creatinine provides a reasonable estimate of GFR.

(Ref. Guyton & Hall 10th Edition, Page-311)

Determination of renal plasma flow from plasma clearance *(PAH clearance)* :

Theoritically, if a substance is *completely* cleared from the plasma, the clearance rate of that substance is equal to the total renal plasma flow. In other words, the amount of the substance delivered to the kidneys (renal plasma flow x Ps) would be equal to the amount excreted in the urine (Us x V).Thus, renal plasma flow (RPF) could be calculated as

$$GFR = \frac{U_s \times V}{P_s}$$

$$= C_s$$

Because the GFR is only about 20 per cent of the total plasma flow, a substance that is completely cleared from the plasma must be excreted by tubular secretion as well as glomerular filtration. There is no known substance that is completely cleared by the kidneys. One substance, However, PAH, is about 90 per cent cleared from the plasma. Therefore, the clearance of PAH can be used as an approximation of renal plasma flow. To be more accurate, one can correct for the percentage of PAH that is still in the blood when it leaves the kidneys. The percentage of PAH removed from the blood is known as the *extraction ratio of PAH* and averages about 90 per cent in normal kidneys. In diseased kidneys, this extraction ratio may be reduced because of inability of damaged tubules to secrete PAH into the tubular fluid.

The calculation of renal plasma flow can be demonstrated by the following example : Assume that the plasma concentration of PAH is 0.01 mg/ml, urine concentration is 5.85 mg/ml, and urine flow rate is 1 ml/min. PAH clearance can be calculated from the rate of urinary PAH excretion (5.85 mg/ml x 1 ml/min) divided by the plasma PAH concentration (0.01 mg/ml). Thus, clearance of PAH calculates to be 585 ml/min.

If the extraction ratio for PAH is 90 per cent, the actual renal plasma flow can be calculated by dividing 585 ml/min by 0.9, yielding a value of 650 ml/min. Thus, total renal plasma flow can be calculated as

Total renal plasma flow = Clearance of PAH/Extraction ratio of PAH.

The extraction ratio (E_{PAH}) is calculated as the difference between the renal arterial PAH(P_{PAH}) and renal venous PAH (V_{PAH}) concentrations, divided by the renal arterial PAH concentration :

$$E_{PAH} = \frac{P_{PAH} - V_{PAH}}{P_{PAH}}$$

(Ref. Guyton & Hall 11th Edition, Page 345)

Determination of total blood flow : We can calculate the total renal blood flow in each minute from the plasma flow and the hematocrit. If the hematocrit is 45% and the renal plasma flow 650 ml/minute.

The total renal blood flow-

$$= \frac{\text{Renal plasma flow}}{1 - \text{hematocrite}}$$

$$= \frac{650}{1 - 45/100}$$

$$= \frac{650 \times 100}{55}$$

= 1182 ml/minute.

(Ref. Guyton & Hall 11th Edition, Page 346)

Plasma Load

The plasma load of a substances means the total amount of that substance present in plasma, that passes through the kindey in each minute.

The plasma concentration of glucose=100 mg/100 ml. and 650 ml of plasma passes through each kidney/min.

So, plasma load of glucose = 650 mg/minute.

Tubular Load : The tubular load of a substance is the total amount of the substance that filters through the glomerular membrane into the tubules in each minute.

If 125 ml of glomerular filtrate is formed in each minute with a glucose concentration of 100 mg percent, the tubular load of glucose is 125 mg per minute.

(Ref. Guyton & Hall 11th Edition)

Renal threshold

Definition : Renal threshold of a substance may be defined as the critical concentration of that substances in plasma below which none of it appears in urine but above which progressively larger quantity of it appears in urine.

Normal value : Renal threshold for glucose 180 mg%.

(Ref. Guyton & Hall 11th Edition)

High threshold substances are :

i. Glucose, Potassium (100%).

ii. Water (99%).

iii. Na^+, Cl^- & Ca^{++} (98 - 99%).

The renal threshold for glucose : Means the threshold concentration of glucose in plasma, below which none of glucose appear in urine but above which progressively larger quantity of it appears in urine. The threshold concentration of glucose in plssma is 180 mg%.

Quantifying renal urine concentration and dilution

Free water and Osmolar clearances : The process of concentrating or diluting the urine requires the kidneys to excrete water and solutes somewhat independently. When the urine is dilute, water is excreted in excess of solutes. Conversely, when the urine is concentrated, solutes are excreted in excess of water.

Osmolar clearances : The total clearance of solutes from the blood can be expressed as the osmolar clearance (C_{osm}); this is the volume of plasma cleared of solutes each minute, in the same way that clearance of a single substance is calculated :

$$C_{osm} = \frac{U_{osm} \times V}{P_{osm}}$$

Where U_{osm} is the urine osmolarity, V is the urine flow rate, and P_{osm} is the plasma osmolarity. For example, if plasma osmolarity is 300 mOsm/L, urine osmolarity is 600 mOsm/L, urine flow rate is 1 ml/min (0.001 L/min), the rate of osmolar excretion is 0.6 mOsm/min (600 mOsm/L x 0.001 L/min) and osmolar clearance is 0.6 mOsm/min divided by 300 mOsm/L, or 0.002 L/min (2.0 ml/min). This means that 2 milliliters of plasma are being cleared of solute each minute.

Free water clearance : Free-water clearance (C_{H_2O}) is calculated as the difference between water excretion (urine flow rate) and osmolar clearance.

$$C_{H_2O} = V - C_{osm}$$

$$= V - \frac{U_{osm} \times V}{P_{osm}}$$

Relative rates at which solutes and water are excreted can be assessed using the concept of 'Free-Water Clear' : The rate of free-water clearance represents the rate at which solute-free water is excreted by the kidneys. When *free-water clearance is positive*, excess water is being excreted by the kidneys; when *free-water clearance is negative*, excess solutes are being removed from the blood by the kidneys and water is being conserved.

Example : Using the example discussed earlier, if urine flow rate is 1 ml/min and osmolar clearance is 2 ml/min, free-water clearance would be- 1 ml/min. This means that instead of water being cleared from the kidneys in excess of solutes, the kidneys are actually returning water back to the systemic circulation, as occurs during water deficits. Thus, *whenever urine osmolarity is greater than plasma osmolarity, free-water clearance will be negative, indicating water conservation.*

When the kidneys are forming a dilute urine (that is, urine osmolarity is less than plasma osmolarity), free-water clearance will be a positive value, denoting that water is being removed from the plasma by the kidneys in excess of solutes. Thus, water free of solutes, called "free water," is being lost from the body and the plasma is being concentrated when free-water clearance is positive.

(Ref. Guyton & Hall 11th Edition; Page-357)

Tubular transport maximum (Tm)

Definition : Almost every actively reabsorbed or secreted substance has a maximum rate at which it can be reabsorbed or secreted in the kidney tubule. The rate at which the substance reabsorbed or secreted in the kidney tubule is called tubular transport maximum.

Example :

Substance	*Transport maximum*
1. Glucose	375 mg/minute
2. Phosphete	0.10 mM/minute
3. Sulphate	0.06 mM/minute
4. Amino acids	1.5 mM/minute
5. Urate	15 mg/minute
6. Lactate	75 mg/minute
7. Plasma protein	30 mg/minute.

Transport maximums for substances that are actively secreted :

Substance	*Transport maximum*
1. Creatinine	16 mg/minute
2. Paraminohippuric acid	80 mg/minute.

Tm of glucose = 375 mg/minute :

Tm of glucose 375 mg/minute means that 375 mg glucose is reabsorbed its maximum rate through the tubules in each minute. If the rate is above this value then glucose is excreted out through urine.

(Ref. Guyton & Hall 11th Edition, page 331)

Glomerulotubular balance

Under normal conditions almost a constant percentage, about 65 percent, of both the sodium and fluid is reabsorbed during passage through the proximal tubules regardless of the rate at which glomerular filtrate enters the tubular system, is called glomerulo tubular balance. That is when GFR increases reabsorption also increases, but when GFR decreases reabsorption also decreases maintaining the proportional balance very near to 65%.

i. *Cause* :
   a. Greater stretch of the tubules.
   b. Higher flow rates.

ii. *Importance* : It helps to prevent overloading of the more distal segments of the tubular system when the GFR increases.

(Ref. Guyton & Hall 11th Edition)

Filtration, reabsorption, and excretion rates of different substances by the kidneys

Some substances, such as glucose and amino acids, are almost completely reabsorbed from the tubules, so that the urinary excretion rate is essentially zero. Many of the ions in the plasma, such as sodium, chloride, and bicarbonate, are also highly reabsorbed, but their rates of reabsorption and urinary excretion are variable, depending on the needs of the body. Certain waste products, such as urea and creatinine, on the other hand, are poorly reabsorbed from the tubules and excreted in reatively large amounts. Therefore, by controlling the rate at which they reabsorb different substances, the kidneys regulate the excretion of solutes independently of one another, a capability that is essential for precise control of the composition of body fluids.

Urinary excretion = Glomerular filtration - Tubular reabsorption + Tubular secretion.

(Ref. Guyton & Hall 11th Edition, page 327)

Example :

	Amount Filtered	*Amount Reabsorbed*	*Amount Excreted*	*% of Filtered Load Reabsorbed*
Glucose(gm/day)	180	180	0	100
Bicarbonate(mEq/day)	4,320	4,318	2	>99.9
Sodium(mEq/day)	25,560	25,410	150	99.4
Chloride(mEq/day)	19,440	19,260	180	99.1
Urea (gm/day)	46.8	23.4	23.4	50
Creatinine(gm/day)	1.8	0	1.8	0

(Ref. Guyton & Hall 11th Edition, page 327)

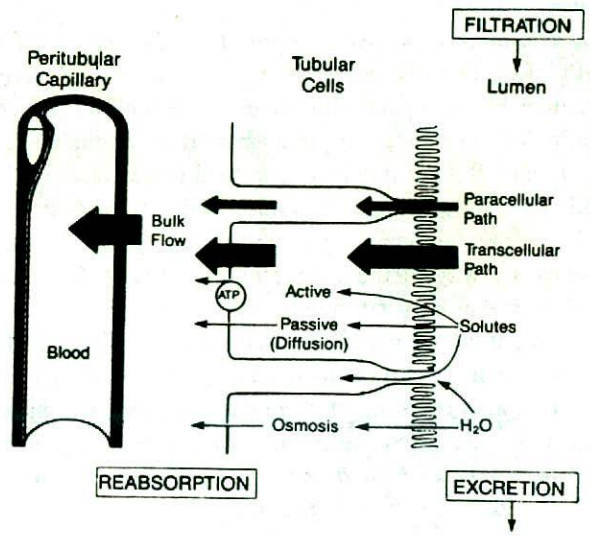


Fig. 13-3. Reabsorption of filtered water and solutes from the tubular lumen across the tubular epithelial cells, through the renal interstitium, and back into the blood. Solutes are transported through the cells (transcellular route) by passive diffusion or active transport or between the cells (paracellular route) by diffusion. Water is transported through the cells and between the tubular cells by osmosis. Transport of water and solutes from the interstitial fluid into the peritubular capillaries occurs by ultrafiltration (bulk flow).

Tubular Reabsorption

Pathway : For a substance to be reabsorbed, it must first be transported -

a. Across the tubular epithelial membranes into the renal interstitial fluid.

b. Through the peritubular capillary membrane back into the blood.

Thus, reabsorption of water and solutes includes a series of transport steps. Reabsorption across the tubular epithelium into the interstitial fluid includes active or passive transport. For instance-

1. *Transcellular route* : Water and solutes can be transported either through the cell membranes themselves.
2. *Paracellular route* : Through the junctional spaces between the cells .
3. *Ultrafiltration (bulk flow)* : After absorption across the tubular epithelial cells into the interstitial fluid, water and solutes are transported the rest of the way through the peritubular capillary walls into the blood by ultrafiltration (bulk flow) that is mediated by hydrostatic and colloid osmotic forces.

The peritubular capillaries behave very much like the venous ends of most other capillaries because there is a net reabsorptive force that moves the fluid and solutes from the interstitium into the blood.

(Ref. Guyton & Hall 11th Edition, Page 328)

Solutes can be transported through epithelial cells or between cells : Renal tubular cells, like other epithelial cells, are held together by tight junctions. Lateral intercellular spaces lie behind the tight junctions and separate the epithelial cells of the tubule. Solutes can be reabsorbed or secreted across the cells by way of the transcellular pathway or between the cells by moving across the tight junctions and intercellular spaces, by way of the paracellular pathway. ***Sodium*** is a substance that moves through both routes, although most of the sodium is transported through the transcellular pathway. In some nephron segments, especially the proximal tubule, ***water*** is also reabsorbed across the paracellular pathway, and substances dissolved in the water, especially ***potassium, magnesium, and chloride ions***, are carried with the reabsorbed fluid between the cells.

(Ref. Guyton & Hall 11th Edition, Page 329)

Tubular reabsorption includes- Active and Passive Transport

Active transport : A good example of *primary active transport* is sodium potassium ATPase pump. Reabsorption of glucose by the renal tubule is an example of *secondary active transport*. Although solutes can be reabsorbed by active and/or passive mechanisms by the tubule, water is always reabsorbed by a passive (nonactive) physical mechanism called *osmosis*, which means water diffusion from a region of low solute concentration (high water concentration) to one of high solute concentration (low water concentration).

(Ref. Guyton & Hall 11th Edition, Page 328)

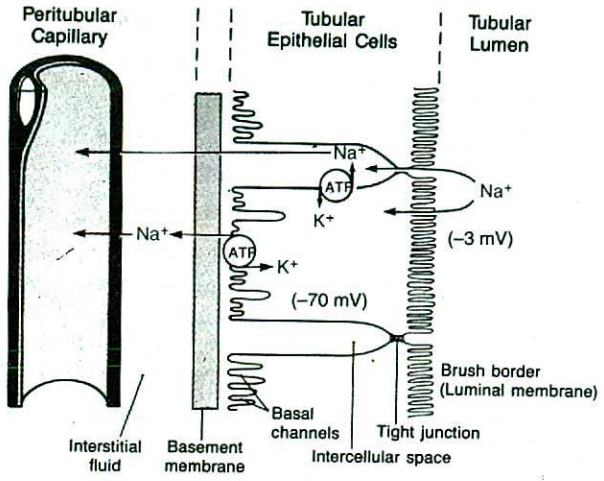


Figure 13-4. Basic mechanism for active transport of sodium through the tubular epithelial cell. The sodium-potassium pump transports sodium from the interior of the cell across the basolateral membrane, creating a low intracellular sodium concentration and a negative intracellular electrical potential. The low intracellular sodium concentration and the negative electrical potential cause sodium ions to diffuse from the tubular lumen into the cell through the brush border.

1. **Primary active transport through the tubular membrane is linked to hydrolysis of ATP** : A good example of a primary active transport system is the ***reabsorption of sodium ions*** across the proximal tubular membrane.

   Active reabsorption of sodium by sodium-potassium ATPase occurs in most parts of the tubule. In certain parts of the nephron, there are additional provisions for moving large amounts of sodium into the cell. In the *proximal tubule*, there is an extensive brush border on the luminal side of the membrane (the side that faces the tubular lumen) that multiplies the surface area about 20-fold. There are also sodium carrier proteins that bind sodium ions on the luminal surface of the membrane and release them inside the cell, providing facilitated diffusion of sodium through the membrane into the cell. These sodium carrier proteins are also important for secondary active transport of other substances, such as glucose and amino acids.

   Thus, the net reabsorption of sodium ions from the tubular lumen back into the blood involves at least three steps :

   i. Sodium is transported across the basolateral membrane against an electrochemical gradient by the *sodium-potassium ATPase pump.*

   ii. Sodium diffuses across the luminal membrane (also

called the apical membrane) into the cell down an electrochemical gradient established by the sodium-potassium ATPase pump on the basolateral side of the membrane.

iii. Sodium, water, and other substances are reabsorbed from the interstitial fluid into the peritubular capillaries by *ultrafiltration*, a passive process driven by the hydrostatic and colloid osmotic pressure gradients.

(Ref. Guyton & Hall 11th Edition, Page 328)

2. **Secondary active reabsorption through the tubular membrane** : Secondary active transport of glucose and amino acids occurs in the proximal tubule. In both instances, a specific carrier protein in the brush border combines with a sodium ion and an amino acid or a glucose molecule at the same time. These transport mechanisms are so efficient that they remove virtually all the glucose and amino acids from the tubular lumen. After entry into the cell, glucose and amino acids exit across the basolateral membranes by *facilitated diffusion*, driven by the high glucose and amino acid concentrations in the cell.

   For ***glucose reabsorption***, *secondary active transport* occurs at the luminal membrane, but *passive facilitated diffusion* occurs at the basolateral membrane, and *passive uptake by bulk flow* occurs at the peritubular capillaries.

   (Ref. Guyton & Hall 11th Edition, Page 329)

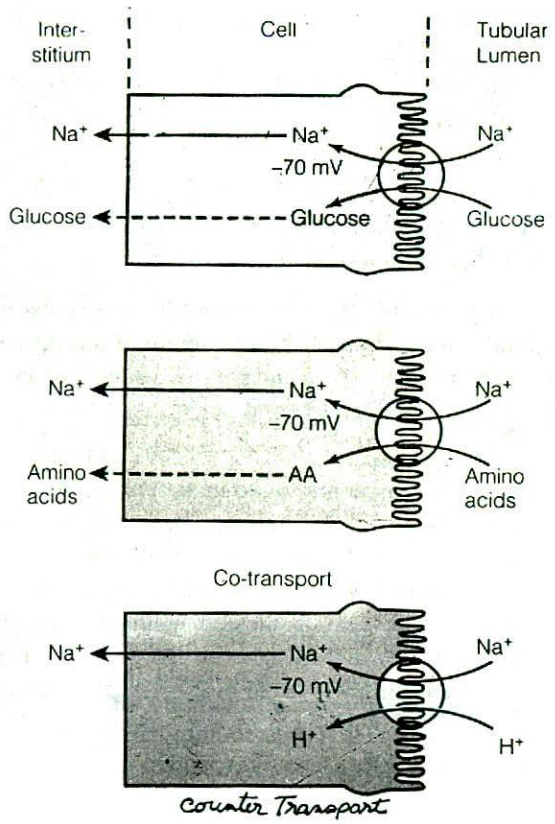


Figure 13-5. Mechanisms of seecondary active transport. The upper two cells show the co-transport of glucose or amino acids along with sodium ions through the brush border of the tubular epithelial cells, followed by facilitated diffusion through the basolateral membranes. The third cell shows the counter-transport of hydrogen ions from the interior of the cell across the brush border member and into the tubular lumen; movement of sodium ions into the cell, down an electrochemical gradient established by the sodium-potassium pump of the basolateral membrane, provides the energy for transport of the hydrogen ions from inside the cell into the tubular lumen

3. **Secondary active secretion into the tubules** : A few substances are secreted into the tubules by secondary active transport. This often involves counter-transport of the substance with sodium ions.

   One example of counter-transport, shown in *figure 10-6*, is the *active secretion of hydrogen ions* coupled to sodium reabsorption in the luminal membrane of the proximal tubule. In this case, sodium entry into the cell is coupled with hydrogen extrusion from the cell by sodium-hydrogen counter-transport. This transport is mediated by a specific protein in the brush border of the luminal membrane. As sodium is carried to the interior of the cell, hydrogen ions are forced outward in the opposite direction into the tubular lumen.

   (Ref. Guyton & Hall 11th Edition, Page 330)

4. **Pinocytosis *(An active transport mechanism for reabsorption of proteins)*** : Some parts of the tubule, especially the proximal tubule, reabsorb large molecules such as ***proteins*** by *pinocytosis*. In this process, the protein attaches to the brush border of the luminal membrane, and this portion of the membrane then invaginates to the interior of the cell until it is completely pinched off and a vesicle is formed containing the protein. Once inside the cell, the protein is digested into its constituent amino acids, which are reabsorbed through the basolateral membrane into the cell.

   (Ref. Guyton & Hall 11th Edition, Page 330)

Reabsorption and Secretion
along different parts of the nephron

Proximal tubular reabsorption : Nomally, about 65 per cent of the filtered load of sodium and water and a slightly lower percentage of filtered chloride are reabsorbed by the proximal tubule before the filtrate reaches the loops of Henle. These pecentages can be increased or decreased in different phsiological conditions.

The proximal tubules have a high capacity for active and passive reabsorption : The high capacity of the proximal tubule for reabsorption results from its special cellular characteristics, as shown in figure . The poximal tubule epithelial cells are highly metabolic and have large numbers of mitochondria to support potent active transport processes. In addition, the proximal tubular cells have an extensive brush border on the

luminal (apical) side of the membrane as well as an extensive labyrinth of intercellular and basal channels, all of which together provide an extensive membrane surface area on the luminal and basolateral sides of the epithelium for rapid transport of sodium ions and other substances.

The extensive membrane surface of the epithelial brush border is also loaded with protein carrier molecules that transport a large fraction of the sodium ions across the luminal membrane linked by way of the co-transport mechanism with multiple organic nutrients such as amino acids and glucose. The remainder of the sodium is transported from the tubular lumen into the cell by counter-transport mechanisms, which reabsorb sodium while secreting other substances into the tubular lumen, especially hydrogen ions. The secretion of hydrogen ions into the tubular lumen is an important step in the removal of bicarbonate ions from the tubule (by combining H^+ with the HCO_3^- to form H_2CO_3, which then dissociates into H_2O and CO_2).

Although the sodium-potassium ATPase pump provides the major force for reabsorption of sodium, chloride, and water throughout the proximal tubule, there are some differences in the mechanisms by which sodium and chloride are transported through the luminal side of the early and late portions of the proximal tubular membrane.In the *first half of the proximal tubule*, sodium is reabsorbed by co-transport along with glucose, amino acids, and other solutes. But in the *second half of the proximal tubule,* little glucose and amino acids remain to be reabsorbed. Instead, sodium is now reabsorbed mainly with chloride ions. The second half of the proximal tubule has a relatively high concentration of chloride (around 140 mEq/L) compared with the early proximal tubule (about 105 mEq/L) because when sodium is reabsorbed, it preferentially carries with it glucose, bicarbonate, and organic ions in the early proximal tubule, leaving behind a solution that has a higher concentration of chloride. In the second half of the proximal tubule, the higher chloride concentration favors the diffusion of this ion from the tubule lumen through the intercellular junctions into the renal interstitial fluid.

(Ref. Guyton & Hall 11th Edition, Page 333)

Concentrations of solutes along the proximal tubule : The amount of sodium in the tubular fluid decreases markedly along the proximal tubule, the *concentration* of sodium (and the total osmolarity) of the proximal tubules is so great that water reabsorption keeps place with sodium reabsorption. Certain organic solutes, such as glucose, amino acids, and bicarbonate are much more avidly reabsorbed than water, so that their concentrations decrease markedly along the length of the proximal tubule. Other organic solutes that are less permeant and not actively reabsorbed, such as urea, increase their concentration along the proximal tubule. The total solute concentration, as reflected by osmolarity, remains essentially the same all along the proximal tubule because of the extremely high permeability of this part of the nephron to water.

(Ref. Guyton & Hall 11th Edition, Page 334)

Secretion of organic acids and bases by the proximal tubule : The *proximal tubule* is also an important site for secretion of organic acids and bases such as *bile salts, oxalate, urate, and catecholamines*. Many of these substances are the end products of metabolism and must be rapidly removed from the body. The *secretion* of these substances into the proximal tubule plus *filtration* into the proximal tubule by the glomerular capillaries and the almost total lack of reabsorption in any portion of the tubular system, all combined, contribute to rapid excretion in the urine.

Another compound that is rapidly secreted by the proximal tubule is *para-aminohippuric acid (PAH)*. PAH is secreted so rapidly that the normal person can clear about 90 per cent of the PAH from the plasma flowing through the kidneys and excrete it in the urine. For this reason, the rate of PAH clearance can be used as an index of the renal plasma flow.

(Ref. Guyton & Hall 11th Edition, Page 334)

Solute and water transport in the Loop of Henle : The loop of Henle consists of three functionally distinct segments :

a. Descendtng thin segment
b. Ascending thin segment
c. Thick ascending segment.

The thin descending and thin ascending segments, as their names imply, have thin epithelial membranes with no brush borders, few mitochondria, and minimal levels of metabolic activity.

The *descending part of the thin segment* is highly permeable to water and moderately permeable to most solutes, including urea and sodium. The function of this nephron segment is mainly to allow simple diffusion of substances through its walls. About 20 per cent of the filtered water is reabsorbed in the loop of Henle, and almost all of this occurs in the descending thin limb because the ascending limb, including both the thin and the thick portions, is virtually impermeable to water, a characteristic that is important for concentrating the urine.

The *thick segment of the loop of Henle,* which begins about half way up the ascending limb, has thick epithelial cells that have high metabolic activity and are capable of active reabsorption of sodium, chloride, and potassium. About 25 per cent of the filtered loads of sodium, chloride , and potassium are reabsorbed in the loop of Henle, mostly in the thick ascending limb. Considerable amounts of other ions, such as calcium, bicarbonate, and magnesium, are also reabsorbed in the thick ascending loop of Henle. The thin segment of the ascending limb has a much lower reabsorptive capacity than the thick

segment, and the descending thin limb does not reabsorb significant amounts of any of these solutes.

An important component of solute reabsorption in the thick ascending limb is the sodium-potassium ATPase pump in the epithelial cell basolateral membranes. As in the proximal tubule, the reabsorption of other solutes in the thick segment of the ascending loop of Henle is closely linked to the reabsorptive capability of the sodium potassium ATPase pump, which maintains a low intracellular sodium concentration. The low intracellular sodium concentration in turn provides a favorable gradient for movement of sodium from the tubular fluid into the cell. In the thick ascending loop, movement of sodium across the luminal membrane is mediated primarily by a *1- sodium, 2-chloride, 1-potassium* co-transporter . This co-transport protein carrier in the luminal membrane uses the potential energy released by downhill diffusion of sodium into the cell against a concentration gradient.

The thick ascending limb also has a sodium-hydrogen counter-transport mechanism in its luminal cell membrane that mediates sodium reabsorption and hydrogen secretion in this segment.
Because the thick segment of the ascending loop of Henle is virtually impermeable to water, most of the water delivered to this segment remains in the tubule, despite reabsorption of large amounts of solute. Thus, the tubular fluid in the ascending limb becomes very dilute as it flows toward the distal tubule, a feature that is important in allowing the kidneys to dilute or concentrate the urine under different conditions.

(Ref. Guyton & Hall 11th Edition, Page 334, 335)

Distal tubule : The thick segment of the ascending limb of the loop of Henle empties into the distal tubule. The *very first portion* of the distal tubule forms part of the *juxtaglomerular complex* that provides feedback control of GFR and blood flow in this same nephron. The *next early part* of the distal tubule is highly convoluted and has many of the same reabsorptive characteristics of the thick segment of the ascending limb of the loop of Henle. That is, it avidly reabsorbs most of the ions, including sodium, potassium, and chloride, but is *virually impermeable to water and urea.* For this reason, it is referred to as the *diluting segment* because it also dilutes the tubular fluid.

(Ref. Guyton & Hall 11th Edition, Page 336)

Late distal tubule & cortical collecting tubule : The *second half of the distal tubule* and the subsequent *cortical collecting tubule* have similar functional characteristics. Anatomically, they are composed of two distinct cell types, the principal cells and the intercalated cells. The *principal cells* reabsorb sodium and water from the lumen and secrete potassium ions into the lumen. The *intercalated cells* reabsorb potassium ions and secrete hydrogen ions into the tubular lumen.

a. ***The principal cells reabsorb sodium and secrete potassium*** : Sodium reabsorption and potassium secretion by the principal cells depend on the activity of a sodium-potassium ATPase pump in each cell's basolateral membrane. This pump maintains a low sodium concentration inside the cell and, therefore, favors sodium diffusion into the cell through special channels. The secretion of potassium by these cells from the blood into the tubular lumen involves two steps :
   1. Potassium enters the cell because of the sodium-potassium ATPase pump, which maintains a high intracellular potassium concentration.
   2. Once in the cell, potassium diffuses down its concentration gradient across the luminal membrane into the tubular fluid.

b. ***The Intercalated cells avidly secrete hydrogen and reabsorb bicarbonate and potassium ions :***
Hydrogen ion secretion by the intercalatd cells is mediated by a hydrogen-ATPase transport mechanism. Hydrogen is generated in this cell by the action of carbonic anhydrase on water and carbondioxide to form carbonic acid, which then dissociates into hydrogen ions and bicarbonate ions. The hydrogen ions are then secreted into the tubular lumen, and for each hydrogen ion secreted, a bicarbonate ion becomes available for reabsorption across the basolateral membrane. The intercalated cells also reabsorb potassium ions, although the mechanisms are not well understood.

The functional characteristics of the late distal tubule and cortical collecting tubule can be summarized as follows :

1. The tubular membranes of both segments are *almost completely impermeable to urea*, similar to the diluting segment of the early distal tubule; thus, almost all the urea that enters these segments passes on through and into the collecting duct to be excreted in the urine, although some reabsorption of urea occurs in the medullary collecting ducts.
2. Both the late distal tubule and the cortical collecting tubule segments *reabsorb sodium ions*, and the rate of reabsorption is controlled by hormones, especially **aldosterone**. At the same time, these segments secrete potassium ions from the peritubular capillary blood into the tubular lumen, a process that is also controlled by aldosterone and by other factors such as the concentration of potassium ions in the body fluids.
3. The intercalated cells of these nephron segments avidly *secrete hydrogen ions* by an active hydrogen-ATPase mechanism. This process is different from the secondary active secretion of hydrogen ions by the proximal tubule because it is capable of secreting hydrogen ions against a large concentration gradient, as much as 1000 to 1. This is in contrast to the relatively small gradient (4 to 10-fold) for hydrogen ions that can be achieved by secondary active

secretion in the proximal tubule. Thus, the intercalated cells play a key role in acid-base regulation of the body fluids.

4. The permeability of the late distal tubule and cortical collecting duct to water is *controlled by the concentration of ADH*, which is also called vasopressin. *With high levels of ADH, these tubular segments are permeable to water, but in the absence of ADH, they are virtually impermeable to water*. This special characteristic provides an important mechanism for controlling the degree of dilution or concentration of the urine.

(Ref. Guyton & Hall 11th Edition, Page 336, 337)

Medullary collecting duct : Although the medullary collecting ducts reabsorb less than 10 per cent of the filtered water and sodium, they are the final site for processing the urine and, therefore, play an extremely important role in determining the final urine output of water and solutes.

The epithelial cells of the collecting ducts are nearly cuboidal in shape with smooth surfaces and relatively few mitochondria.

Special characteristics of this tubular segment are as follows :

a. The permeability of the medullary collecting duct to water is controlled by the level of ADH. With high levels of ADH, *water* is avidly reabsorbed into the medullary interstitium, thereby reducing the urine volume while at the same time concentrating most of the solutes in the urine.

b. Unlike the cortical collecting tubule, the medullary collecting duct is permeable to *urea*. Therefore, some of the tubular urea is reabsorbed into the medullary interstitium, helping to raise the osmolality in this region of the kidneys and contributing to the kidneys' overall ability to form a concentrated urine.

c. The medullary collecting duct is capable of *secreting hydrogen ions* against a large concentration gradient, as also occurs in the cortical collecting tubule. Thus, the medullary collecting duct also plays a key role in regulating acid-base balance.

(Ref. Guyton & Hall 11th Edition, Page 337, 338)

Summary of urine concentrating mechanism and changes in osmolarity in different segments of the tubules :

1. ***Proximal tubule*** : About 65 per cent of the filtered electrolytes are reabsorbed in the proximal tubule. However the tubular membranes are highly permeable to water, so that whenever solutes are reabsorbed, water also diffuses through the tubular membrane by osmosis. Therefore, the osmolarity of the fluid remains about the same as the glomerular filtrate, 300 mOsm/L.

2. ***Decending Loop of Henle*** : As fluid flows down the decending loop of Henle, water is absorbed into the medulla. The descending limb is highly permeable to water but much less permeable to sodium chloride and urea. Therefore, the osmolarity of the fluid flowing through the descending loop gradually increases until it is equal to that of the surrounding interstitial fluid, which is about 1200 mOsm/L when the blood concentration of ADH is high. When a dilute urine is being formed, owing to low ADH concentrations, the medullary interstitial osmolarity is less than 1200 mOsm/L; consequently the descending loop tubular fluid osmolarity also becomes less concentrated. This is due partly to the fact that less urea is absorbed into the medullary interstitium from the collecting ducts when ADH levels are low and the kidney is forming a large volume of dilute urine.

3. ***Thin ascending Loop of Henle*** : The thin ascending limb is essentially impermeable to water but reabsorbs some sodium chloride. Because of the high concentration of sodium chloride in the tubular fluid, owing to water removal from the descending loop of Henle, there is some passive diffusion of sodium chloride from the thin ascending limb into the medullary interstitium. Thus, the tubular fluid becomes more dilute as the sodium chloride diffuses out of the tubule and water remains in the tubule. Some of the urea absorbed into the medullary interstitium from the collecting ducts also diffuses into the ascending limb, thereby returning the urea to the tubular system and helping to prevent its washout from the renal medulla. This urea recycling is an additional mechanism that contributes to the hyperosmotic renal medulla.

4. ***Thick ascending loop of Henle*** : The thick part of the ascending loop of Henle is also virtually impermeable to water, but large amounts of sodium, chloride, potassium, and other ions are actively transported from the tubule into the medullary interstitium. Therefore, fluid in the thick ascending limb of the Loop of Henle becomes very dilute, falling to a concentration of about 100 mOsm/L.

5. ***Early distal tubule*** : The early distal tubule has properties similar to those of the thick ascending loop of Henle, so that further dilution of the tubular fluid occurs as solutes are reabsorbed while water remains in the tubule.

6. ***Late distal tubule and cortical collecting tubules*** : In the late distal tubule and cortical collecting tubules, the osmolarity of the fluid depends on the presence or absence of ADH. With high levels of ADH, these tubules are highly permeable to water, and significant amounts of water are reabsorbed. Urea, however, is not very permeant in this part of the nephron, resulting in increased urea concentration as water is reabsorbed. This allows most of the urea delivered to the distal tubule and collecting tubule to pass into the inner medullary collecting ducts, from which it is eventually reabsorbed or excreted in the urine. In the absence of ADH, little water is reabsorbed in the late distal tubule and cortical collecting tubule; therefore, osmolarity decreases even

further because of continued active reabsorption of ions from these segments.

7. ***Inner medullary collecting ducts*** : The concentration of fluid in the inner medullary collecting ducts also depends on- i. ADH and ii. the osmolarity of the medullary interstitium established by the countercurrent mechanism. In the presence of large amounts of ADH, these ducts are highly permeable to water, and water diffuses from the tubule into the interstitium until osmotic equilibrium is reached, with the tubular fluid having about the same concentration as the renal medullary interstitium (1200 to 1400 mOsm/L). Thus, a very concentrated but small volume of urine is produced when ADH levels are high. Because water reabsorption increases urea concentration in the tubular fluid, and because the inner medullary collecting ducts are highly permeable to urea, much of the highly concentrated urea in the ducts diffuses out of the tubular lumen into the medullary interstitium. This absorption of the urea into the renal medulla contributes to the high osmolarity of the medullary interstitium and the high concentrating ability of the kidney.

There are several important points to consider that may not be obvious from this discussion :

i. *First*, although sodium chloride is one of the principal solutes that contributes to the hyperosmolarity of the medullary interstitium, *the kidney can, when needed, excrete a highly concentrated urine that contains little sodium chloride*. The hyperosmolarity of the urine in these circumstances is due to high concentrations of other solutes, especially of waste products such as urea and creatinine. One condition in which this occurs is dehydration accompanied by low sodium intake. Low sodium intake stimulates formation of the hormones angiotensin II and aldosterone, which together cause avid sodium reabsorption from the tubules while leaving the urea and other solutes to maintain the highly concentrated urine.

ii. *Second, large quantities of dilute urine can be excreted without increasing the excretion of sodium*. This is accomplished by decreasing ADH secretion, which reduces water reabsorption in the more distal tubular segments without significantly altering sodium reabsorption.

iii. *Finally*, we should keep in mind that there is an *obligatory urine volume*, which is dictated by the maximum concentrating ability of the kidney and the amount of solute that must be excreted. Therefore, if large amounts of solute must be excreted, they must be accompanied by the minimal amount of water necessary to excrete them. For example, if 1200 milliosmoles of solute must be excreted each day, this requires at least 1 liter of urine if maximal urine concentrating ability is 1200 mOsm/L.

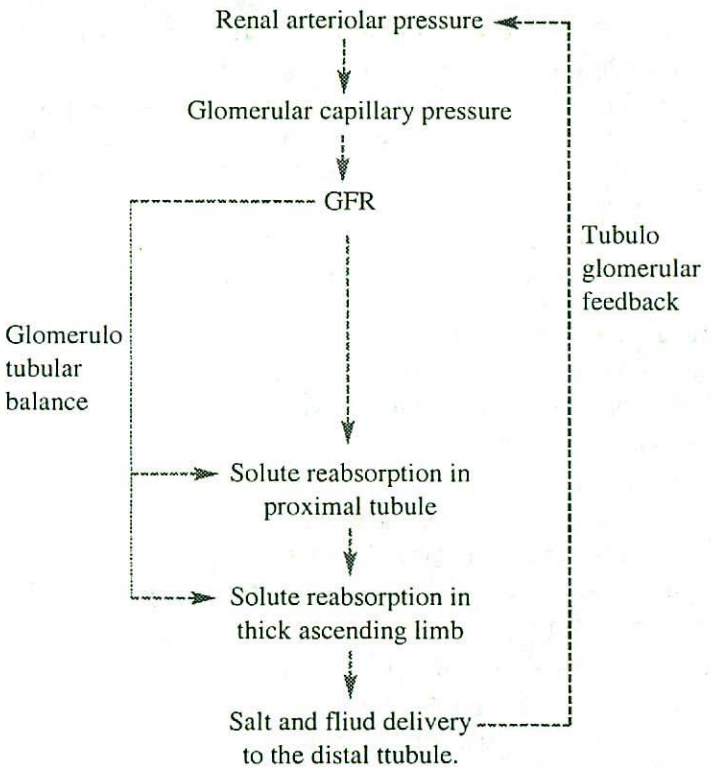
(Ref. Guyton & Hall 11th Edition, Page 355)

Reabsoption & Secretion in the renal tubule

1. Reabsorbed substances : Na^+, K^+, Ca^{++}, Mg^{++}, glucose,amino acids, vitamins, acetoacetone ion, Cl^-, HCo_3^-, So_4^{--}, NO_3^-, PO_4^{-3}, urea etc.
2. Secreted substances : K^+, H^+, ammonia, creatinine, P-aminohippuric acid, penicillin, bromsulphthelin, diodrast etc.
3. Completely reabsorbed substances are : Glucose, proteins, amino acids, acetoacetate ions, and vitamins.
4. Non-reabsorbed substances are : Creatinine, inulin, manitol and sucrose.

(Ref. Guyton & Hall 11th Edition)

Mechanisms of glomerulotubular balance and tubuloglomerular feedback



(Ref. Ganong 22th Edition; Page 713)

Reabsorbtion of water

Passive water reabsorption by osmosis is coupled mainly to sodium reabsorption : When solutes are transported out of the tubule by either primary or secondary active transport, their concentrations tend to decrease inside the tubule while increasing in the renal interstitium. This creates a concentration difference that causes osmosis of water in the same direction that the solutes are transported, from the tubular lumen to the renal interstitium. Some parts of the renal tubule, especially the proximal tubule, are highly permeable to water, and water reabsorption occurs so rapidly that there is only a small concentration gradient for solutes across the tubular membrane.

A large part of the osmotic flow of water occurs through the so-called tight junctions between the epithehal cells as well as through the cells themselves. The reason for this is that the junctions between the cells are not as tight as their name would imply, and they allow significant diffusion of water and small ions. This is especially true in the proximal tubules, which have a high permeability for water and a smaller but significant permeability to most ions, such as sodium, chloride, potassium, calcium, and magnesium.

(Ref. Guyton & Hall 11th Edition, Page 332)

Reabsorbtion of water takes place through out the tubule except ascending limb of loop of Henle by passive diffusion :

i. In the *proximal convoluted tubule*, obligatory reabsorbtion of water takes place along with the active reabsorption of Na.

ii. In *descending limb of loop of Henle* water reabsorption takes place by diffusion.

iii. In *distal convoluted tubule*, facultative water reabsorption occurs. Here anti-diuretic hormone (ADH) increase the permeability of distal convoluted tubular cell which causes water reabsorption.

iv. In *collecting tubule* water reabsorption takes place under the influence of antidiuretic hormone(ADH).

Renal handling of water

Normally about 99.3% of the filtered load of water is reahsorhed in the renal tubular system with excretion of averages 1 ml/minute urine.

I. *Mechanisms* :
   i. Passive reabsorption along the osmotic gradients set up by the active transport of solutes.
   ii. Anti-diuretic-hormone (ADH) dependent H_2O reabsorption.

II. *Reabsorption at different parts of the tubules* :
   i. *PCT* : About 65 - 80% of the filtered water is reabsorbed. Osmolarity : isotonic (300 mosmol/L).
   ii. *Descending limb of loop of Henle* : About 15% water is reabsorhed passively with no solute reabsorption. This makes the isosmotic tubular fluids into hyperosmotic solution.
   Osmolarity : At the tip of the LH the osmolarity reaches to some 1200 to 1400 mosmole/ L.
   iii. *Ascending limb of loop of Henle* : Is impermeable to H_2O but highly permeable to Na^+, Cl^- and urea. This makes the hyperosmotic tubular fluid into hyposmotic solution.
   Osmolarity :
      a. Thin segment- tonicity gradually decreases
      b. Thick segment- hypotonic- 100 mosmol/L.
   iv. *Diluting segment of the distal tubule* : Is impermeable to H_2O but highly permeable to Na^+, Cl^- and urea.
   Osmolarity : More hypotonic.
   v. *Late distal tubule and collecting system* :
      a. Late distal tubule : 5-10% of H_2O is reabsored. H_2O reabsorption depends on the presence of circulating ADH.
      b. Collecting system : 14.7% water is reabsored. H_2O reabsorption depends on the presence of circulating ADH. Thus only 0.5 to 1.5 liters of urine is excreted per day. About 2% is reabsorbed in the absence of ADH.
      Osmolarity :
         a. Hypertonic (upto 1400 mosmol/L) in presence of ADH
         b. Hypotonic (below to 30 mosmol/L) in absence of ADH.

Among 125 ml/min. of glomerular filtrate : Water that is reabsorbed in each segment of the tubules as follows :

a. Proximal tubules : 65%
b. Loop of Henle : 15%
c. Distal tubules : 10%
d. Collecting ducts : 9.3%
e. Passing into the urine : 0.7%

Difference between obligatory and facultative water reabsorption.

Obligatory	*Facultative*
i. It takes place in the PCT.	i. It takes place in the DCT and CT.
ii. It occurs along with the reabsorption of (electrolyte) Na^+.	ii. It occurs under the influence of ADH.
iii. Rate of reabsorption is proportional to GF of the iso-osmotic condition.	iii. Rate of reabsorption is proportional to the ADH secretion.

Obligatory water reabsorption : When the water reabsorption occurs at such a rate that the iso-osmotic condition of glomerular filtrate is maintained in the proximal convoluted tubles, reabsorption of Na^+ from the tubules into in the peritubular fluid of intercellular spaces increases its osmotic pressure while that in the tubules decreases. Since the proximal tubular membrane is highly permeable to water, osmosis of water occur into peritubular fluid from the tubules. It is called obligatory reabsorption of water.

Facultative reabsorption of water : When water reabsorbtion occurs under the influence of Anti-diuretic hormone (ADH).

The distal and collecting tubules are normally impermeable to water. Here water reabsorbtion takes place under the influence of ADH. Anti diuretic hormone itself acts not on the luminal membrane of the tubular epithelial cells but instead on the basolateral membrane of the these cells. It activates the enzyme adenyl cyclase in the membrane, which then causes formation of cyclic adenosine monophosphate (cyclic AMP) in the cell cytoplasm. The cyclic AMP then diffuses to the luminal membrane of the cells where it greatly increases the permeability to water, causes osmosis of water. This is called facultiative water reabsorption.

(Ref. Guyton & Hall 11th Edition)

Tubular handling of sodium

The filtered load of Na^+ is approximately 25,200 mmol per day. About 99.3% of this filtered load is reabsorbed in the renal tubular system with only excretion of 200 - 250 mmol daily in the urine.

The reabsorption of Na^+ occurs by the following mechanism :

i. *Active transport process (co-transport and antiport)* : In the PCT, the thick segment of ALLH, the DTs and the CDs Na^+ moves by co-transport (with glucose, amino acids) process. Na^+ reabsorption is equivalent to Cl^- reabsorption plus H^+ and K^+ secretion into the tubular fluid.

The transport mechanism in the thick ALLH depends on a carrier that transports one Na^+ one K^+ and 2 Cl^- from the tubular lumen into the cells. Na^+-K^+ ATPase actively transports the Na^+ out of the cells into the interstitium.

ii. *Passive reabsorption of Na+* : In the thin segment of the ALLH NaCl is passively reabsorbed.

iii. *Cation exchange process* : In the distal tubules and collecting system Na^+ is reabsorbed by two electrically linked cation exchange processes :

a. Na^+- H^+ exchange involves Na^+ reabsorption and H^+ secretion

b. Na^+-K^+ exchange involves Na^+ reabsorption and K^+ secretion.

These cation exchange processes is competitive (i.e. K^+ competes with H^+ for Na^+). Both cation exchange processes, however, are enhanced by hormone aldosterone.

Mechanism of tubular reabsorption of Na^+ :

Site of reabsorption	*Mechanism*
a. Proximal tubule	a. Active transport
b. ALLH (thick)	b. Co- transport (Na^+-K^+-2Cl)
c. ALLH (thin)	c. Passive transport
d. Distal tubule	d. Aldosterone induced
e. Collecting ducts	e. Countertrausport.

Aldosterone induced Na^+ reabsorption

It enhances the reabsorption of Na^+ from the distal tubule and the collecting system (only 2- 3%). Of the amount of filtered Na^+ only 2- 3% are actively reabsorbed via an aldosterone-dependent cation exchange mechanism in the distal nephron. Aldosterone acts by the following way in this regard :

a. Formation of hormone receptor complex : Upon entering into the tubular epithelial cells aldosterone binds with cytoplasmic receptors to form hormone receptor complex

b. DNA activation and messenger RNA formation : Hormone receptor complex activates DNA and form mRNA by transcription process.

c. Formation of biologically active protein by mRNA : Messenger RNA comes out of the nucleus and form active protein by the process of translation.

d. Protein molecule increases Na^+ permeability by the following ways :

i. *Permease hypothesis* : Protein increases passive permeability of the cell to Na^+.

ii. Metabolic hypothesis : Protein increases the oxidation of substrate to provide ATP.

iii. Pump hypothesis : Protein acts directly to increase the activity of the pump. In any case the effect is increased active transport of Na from the tubular lumen to interstitial space.

Salt appetite mechanism for controlling ECF sodium concentration and volume : Maintenance of normal extracellular fluid volume and sodium concentration requires a balance between sodium excretion and sodium intake. In modern civilizations, sodium intake is almost always greater than necessary for homeostasis. In fact, the average sodium intake for individuals in industrialized cultures eating processed foods usually ranges between 100 and 200 mEq/day, even though humans can survive and function normally on 10 to 20 mEq/day. Thus, most people cat far more sodium than is necessary for homeostasis, and there is evidence that our usual high sodium intake may contribute to cardiovascular disorders such as *hypertension*.

Salt appetite is due in part to the fact that animals and humans like salt and eat it regardless of whether they are salt-deficient. There is also a regulatory component to salt appetite in which there is a behavioral drive to obtain salt when there is sodium deficiency in the body. This is particularly important in herbivores, which naturally eat a low-sodium diet, but salt craving may also be important in humans who have extreme deficiency of sodium, such as occurs in Addison's disease. In this instance, there is deficiency of aldosterone secretion, which causes excessive loss of sodium in the urine and leads to decreased extracellular fluid volume and decreased sodium concentration; both of these changes elicit the desire for salt.

In general, *the two primary stimuli that are believed to excite salt appetite are* :

i. Decreased extracellular fluid sodium concentration
ii. Decreased blood volume or blood pressure, associated with circulatory insufficiency.

These are the common major stimuli that elicit thirst.

The neuronal mechanism for salt appetite is analogous to that of the thirst mechanism. Some of the same neuronal centers in the AV3V region of the brain seem to be involved, because lesions in this region frequently affect both thirst and salt appetite simultaneously in animals. Also, circulatory reflexes elicited by low blood pressure or decreased blood volume affect both thirst and salt appetite at the same time.

(Ref. Guyton 10th Edition; page 363)

Quantitative aspects of Na^+ reabsorption in a normal man on a normal Na^+diet

GFR	125 ml/min	
Plasma HCO_3	27 meq/L	
Plasma Na^+	145 meq/L	
Na^+ filtered per minute	18,125 peq	
Reabsorbed with Cl	14,585 peq	
Reabsorbed while reabsorbing 3375 peq of HCO_3		3,375 peq
Reabsorbed in association with formation of titratable acidity and ammonia		50 peq
Reabsorbed in association with K		50 peq
Total Na^+ reabsorbed per minute		13,000 peq

Table 13-2. Changes in Na^+ excretion that would occur as a result of changes in GFR if there were no concomitant changes in Na^+ reabsorption.

GFR (ml/min)	*Plasma Na^+ (peq/mL)*	*Amount Filtered (peq/min)*	*Amount Reabsorbed (peq/min)*	*Amout Excreted (peq/min)*
125	145	18,125	18,000	125
127	145	18,415	18,000	415
124	145	18,000	18,000	0

Renal handling of urea

Normal plasma level : 2.5 - 6.7 mmol/litre (8-25 mg/dl).

The GFR is normally 125 ml/minute, so daily filtered load of urea is approximately 870 mmol. About 460 mmol is reabsorbed. The daily excretion rate depending upon circumstances ranges 30-70% of the filtered load. Therefore the clearance ratio for urea may vary from 0.3 to 0.7. Urea is both reabsorbed from and secreted into renal tubules.

Thus tubular handling of urea is important for the following facts :

1. Urea increases urine osmolarity i.e formation of concentrated urine by its contribution in the establishment of the osmotic gradient in the medullary pyramids.
2. Urea clearance is a measure of GFR.

Urea reabsorption :

a. *Mechenism* : Reabsorption of urea is always passive, from higher concentration in the urine to a lower concentration in plasma.
b. *Site of reabsorption* :
   i. Proximal convoluted tubule
   ii. Inner portion of the medullary collecting duct (especially in the presence of ADH).
   iii. The decending limb of loop of Henle and thin segment of ascending limb of loop of Henle is permeable to urea.
b. *Site of reabsorption* : Some urea reenters the ALLH.

Renal handling of creatinine

Creatinine derives from muscle cells.

i. Normal serum creatinine value : 0.06 to 0.12 mmol/litre (0.6-1.5 mg/dl).
ii. So daily filtered load of creatinine : 12-15 mmol.
iii. Daily reabsorption : No amount of creatinine is reabsorbed from the renal tubules.
iv. Daily excretion : The clearance of creatinine is 160 ml/minute. A typical adult male excretes about 15 mmol of creatinine per day. Creatinine excretion is, however by both glomerular filtration + tubular secretion (relatively small amount).
v. Significance :
   a. Creatinine clearance is a good measure of GFR.
   b. Creatinine content of the urine falls when body muscle decreases for any reason (for example, from paralysis or muscular dystrophy).
   c. Any rise in serum creatinine is a sensitive indicator of malfunction.

Renal handling of para-aminohippuric acid-PAH

PAH is a derivative of hippuric acid.

i. PAH entered into the tubular fluid by glomerular filtration and tubular secretion. The filtered load of PAH is a linear function of the plasma level, but PAH secretion increases as plasma PAH rises only until a maximal secretion rate is reached.
ii. *Mechenism of secretion* : PAH is secreted actively; an active pump at the peritubular cells help to uptake of PAH from blood to tubular cell.
ii. *Transfer from tubular cell to tubular lumen* : Probably by facilitated diffusion.

Ammonia secretion

Ammonia is produced within the renal tubular epithelial cells

and secreted into tubular lumen. 60% secreted ammonia are derived from metabolism of glutamine and 40% are derived from other amino acids or amines i.e alanine, glycine.

Tubular handling of HCO_3^-

The daily filtered load of HCO_3^- is approximately 4300 to 4500 mmol ($P_{HCO_3^-}$ x GFR). About 99.9 to 100% of the filtered load of HCO_3^- is reabsorbed. The renal threshold for HCO_3^- is around 28 mmol/litre. HCO_3^- appears in the urine and urine becomes alkaline when plasma HCO_3^- concentration ($P_{HCO_3^-}$) exceeds the renal threshold. Reabsorption of HCO_3^- alone cannot maintain normal acid base balance. Therefore kindey can capable of generating new HCO_3^- as well.

HCO_3^- reabsorption : Bicarbonate filtered at the glomerulus must be reabsorbed. Reabsorption of HCO_3^- occurs throughout the nephron except in the descending limb of the loop of Henle. HCO_3^- reabsorption in the proximal tubule is complicated because HCO_3^- cannot diffuse freely across the membrane of the tubular cell, whereas CO_2 diffuses freely. Therefore from the tubular fluid HCO_3^- is entered into the tubular epithelial cells in the form of CO_2.

Process of HCO_3^- reabsorption :

i. Formation of H_2CO_3 in the tubular fluid by combination of secreted H^+ with filtered HCO_3^-.

$$H^+ + HCO_3^- \rightarrow H_2CO_3$$

ii. Dehydration of H_2CO_3 by cabonic anhydrase enzyme.

$$H_2CO_3 \rightarrow H_2O + CO_2$$

iii. Entrance of CO_2 into the tubular epithelial cells.

iv. Formation of H_2CO_3 by cellular carbonic anhydrase.

$$H_2O + CO_2 \rightarrow H_2CO_3$$

v. Dissociation of H_2CO_3.

HCO_3^- is transported into blood across basolateral membrane by a secondary active transport system. H^+ is secreted again into the tubular lumen.

About 90% of the filtered HCO_3^- is reabsorbed into the proximal tubule and 10-15% is reabsorbed in the distal tubule and collecting tubules. Normally 2-3 mmol of HCO_3^- is excreted daily in urine.

i. *HCO_3^- regeneration* : The kidneys generate new HCO_3^- in the renal tubular cell via the hydration of CO_2 and dissociation of H_2CO_3. The amount of new HCO_3^- formed per day is approximately 70-100 mEq. The HCO_3^- that is generated within the tubular cell does not represent filtered HCO_3^-.

ii. *HCO_3^- secretion* : The entire segments of the neprone normally reabsorb HCO_3^- except for the cortical collecting ducts. The type B cells of the collecting ducts secrete HCO_3^- into the tubular lumen by the HCO_3-Cl^- exchange mechanism. This HCO_3^- secreting mechanism is important in metabolic alkalosis.

Tubular handling of K^+

K^+ is the only plasma electrolyte that is both secreted into the renal tubules.

i. The normal plasma value : 3.5 - 5.0 mmol/L.

ii. Daily filtered load : About 600 mmol.

iii. *Daily secretion into tubules* : About 50 mmol. The secretion of K^+ is a function of distal tubule. Secretion is influenced by aldosterone and involves an active transport and a passive diffusion process. The steps of K^+ secretion and the role of aldosterone in K^+ secretion may be summarized as follows :

a. Active transport of K^+ from the interstitial fluid into tubular epithelial cells via the Na^+-K^+ATPase pump.

b. Aldosterone increases the activity of the Na^+-K^+ ATase pump in the basolateral membrane of the distal tubular cells.

* Elevation of the intracellular (K^+) favors the net K^+ diffusion at the luminal membrane down a concentration gradient into the tubular lumen. Aldosterone increases the permeability of the luminal membrane to K^+.

* In the distal tubules, K^+ secretion is generally coupled with Na^+ reabsorption in the presence of aldosterone. Since Na^+ is also reabsorbed in association with H^+ secretion, there is competition between K^+ and H^+ for Na^+. When the total body K^+ is high (i.e. hyperkalaemia), H^+ secretion is inhibited; K^+ secretion and excretion are therefore facilitated. Conversely, in hypokalaemia, K^+ secretion declines.

iv. Reabsorption : About 93-94% of the filtered load of K^+ is reabsorbed fron renal tubules. The tubular reabsorption occurs by a transport in the PCT, ALLH, DT, CD.

iv. Daily excretion : 90 mmol. The excretion increased in :

a. Hyperaldosteronaemia (excess K~ secretion)

b. Metabolic alkalosis

c. Uncontrolled diabetes mellitus

Relationship between plasma K^+ and HCO_3^- reabsorption

HCO_3^- reabsorption depends on H^+ secretion. An increase in intracellular H^+ causes increase tubular H^+ secretion - thus favors HCO_3^- reabsorption. Plasma K^+ concentration affects the intracellular H^+ concentration, therefore, influences HCO_3^- reabsorption. There is an inverse relationship between plasma K^+ and HCO_3^- reabsorption.

i. In hypokalaemia : Low plasma $K^+ \rightarrow$ K^+ efflux with influx of Na^+ & $H^+ \rightarrow$ intracellular acidosis $\rightarrow$ more H^+ secretion $\rightarrow$ more reabsorption of HCO_3^-.

ii. In hyperkalaemia : High plasma $K^+ \rightarrow K^+$ influx with efflux of H^+ & $Na^+ \rightarrow$ intracellular alkalosis $\rightarrow$ less H^+ secretion $\rightarrow$ reduce HCO_3^- reabsorption.

Tubular secretion of H^+

I. *The daily filtered load of H^+* : is very negligible i.e only < 0.1 mmol per day.

II. *Tubular secretion* : Is the main source of H^+ in the tubular fluid. Approximately 43-75 mmol H^+ is secreted into the tubular fluid each day.

III. *Reabsorption* : 98-99% of the secreted H^+ is reabsorbed daily.

IV. *Secretion* : About 5 -60 mmol H^+ is excreted daily.

i. *The significance of secretion into renal tubule* :
   a. To maintain normal plasma HCO_3^-
   b. To maintain normal acid-base status of the body.

ii. *Site of secretion* : H^+ secretion occurs in all parts of the nephron except DLLH. Approximate proportions are :
   a. Proximal convulated tubules : 85%
   b. ALLH and distal tubule : 18%
   c. Collecting ducts : 5%

iii. *Mechanism of H^+ secretion* : H^+ is secreted into the tubular lumen by active transport. The primary reaction that is responsible for the H^+ secretion in the different parts of nephrons is :
   a. Proximal tubule : Na^+-H^+ exchange
   b. Distal tubule : Hormone (aldosterone) induced cation exchange i.e Na^+-H^+ exchange.
   c. Collecting ducts : Na^+-H^+ exchange, H^+-K^+ ATPase pump.

iv. *Fate of secreted H^+ in the tubular fluid* : Within the tubular system three important reactions remove free H^+, permitting continuous H^+ secretion in the tubular fluid is mandatory to maintain acid base homeostasis :
   a. Secreted H^+ reacts with HCO_3^- in the proximal and distal tubular fluid- causing HCO_3^- reabsorption
   b. Secreted H^+ reacts with dibasic phosphate ($HPO4^{--}$) in the distal tubules and collecting ducts- causing formation of monobasic phosphate.
   c. Secreted H^+ reacts with NH_3 to form NH_4^+ in the priximal and distal tubules.

The majority of the secreted H^+ is used to bring about HCO_3^- reabsorption and, therefore is not excreted. The most of the H^+ that is excreted occurs in the form of monobasic phosphate and NH_4^+.

Summary of reabsorption and secretion in different parts of the renal tubules

I. *Proximal convulated tubule* :
   i. Reabsorption in proximal tubule :
      a. Glucose and amino acids: 100%
      b. Sodium : 65%
      c. Water : 65%
      d. Urea : 50%
      e. All filtered potassium
      f. Other electrolytes
   ii. Secretion in proximal tubule :
      a. Variable proton secretion for acid-base regulation
      b. Organic ion secretion.

II. *Distal convulated tubule* :
   i. Reabsorption in distal tubule :
      a. Sodium : Variable, controlled by aldosterone
      b. Chloride : follows passively
      c. Water : Variable,controlled by ADH
   ii. Secretion in distal tubule :
      a. Proton secretion : Variable for acid-base regulation
      b. Potassium : Variable, controlled by aldosterone

II. *Collecting duct* :
   a. Water : Variable, reabsorption controlled by ADH
   b. Proton : Variable secretion for acid-base regulation.

Renal tubular buffer system

a. *Buffer systems* : The continuous secretion of H^+ in the tubular fluid is maintained by the operation of the three important buffer systems :

i. *Bicarbonate buffer* : The concentration of HCO_3^- in plasma, and consequently in the glomerular filtrate, normally about 24 mEq/litre. Therefore, in the proximal tubule, most of the secreted H^+ reacts with HCO_3^- to form H_2CO_3, which dissociates into CO_2 and H_2O.

ii. *Phosphate buffer* : The concentration of HPO_4^{--} in the glomerular filtered is only 1.5 meq/litre, but in the distal tubular fluid it is greatly concentrated due to H_2O reabsorption. Thus phosphate buffer is mainly acts in distal tubule. In the urine hydrogen ions are buffered mainly by the phosphate buffer system.

$$H^+A^- + HPO_4^{--} = A + H_2PO_4$$

iii. *Ammonia buffer* : Renal tubular cells secrete NH_3 in the tubular fluid (own urinary buffer). NH_3 reacts with secreted H^+ to form NH_4^+.

b. *Buffer systems acting in renal tubules* :

Buffer system	*Site of action*
i. Bicarbonate (HCO_3^-/CO_2)	i. Proximal and distal tubule
ii. Phosphate ($HPO_4^{--}/H_2PO_4^-$)	ii. Distal tubule and collecting ducts

iii. Ammonia (NH_3/NH_4^+) and distal tubule. iii. Proximal tubule

c. *Importance of renal tubular buffers* :

i. Maintaining continual H^+ secretion in the tubular fluid : Buffer systems *tied up* H^+ in the urine. If there are no buffers, the limiting pH of urine (4.5) would be reached rapidly, and H^+ secretion would stop. Thus urinary buffers facilitate the H^+ excretion without touching the minimum pH of urine.

ii. Acidification of urine.

iii. Maintenance of acid-base homeostasis.

Buffering in Vivo : Buffering in vivo is of course not limited to the blood. The principal buffers in the blood, interstitial fluid, and intracellular fluid are listed in *Table*. The principal buffers in cerebrospinal fluid and urine are the bicarbonate and phosphate systems.

In metabolic acidosis, only 15-20% of the acid load is buffered by the H_2CO_3-HCO_3 system in the ECF, and most of the remainder is buffered in cells.

In metabolic alkalosis, about 30-35% of the OH^- load is buffered in cells.

In respiratory acidosis and *alkalosis*, almost all the buffering is intracellular.

(Ref. Ganong 22th Edition; Page 733)

Principle buffers in body fluids :

i. Blood : a. $H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$

b. $HProt \rightleftharpoons H^+ + Prot^-$

c. $HHb \rightleftharpoons H^+ + Hb^-$

ii. Interstitial fluid : a. $H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$

iii. Intracellular fluid : a. $HProt \rightleftharpoons H^+ + Prot^-$

b. $H_2PO_4^- \rightleftharpoons H^+ + HPO_4^{2-}$

(Ref. Ganong 22th Edition; Page 733)

When a strong acid is added to the blood, the major buffer reactions are driven to the left. The blood levels of the three 'buffer anions"- Hb^- (hemoglobin), $Prot^-$ (protein), and HCO_3^- -consequently drop. The anions of the added acid are filtered into the renal tubules. They are accompanied ('covered") by cations, particularly Na^+, because electrochemical neutrality is maintained. The renal tubules replace the Na^+ with H^+ and in so doing reabsorb equimolar amounts of Na^+ and HCO_3^-, thus conserving the cations, eliminating the acid, and restoring the supply of buffer anions to normal.

When CO_2 is added to the blood, similar reactions occur, except that since it is H_2CO_3 that is formed, the plasma HCO_3^- rises rather than falls.

(Ref. Ganong 22th Edition; Page 733, 734)

Clinical evaluation of acid-base status

In evaluating disturbances of acid-base balance, it is important to know the pH and HCO_3^- content of arterial plasma. Reliable pH determinations can be made with a pH meter and a glass pH electrode. The HCO_3^- content of plasma cannot be measured directly, but the Pco_2 can be measured with a CO_2 electrode and the HCO_3^- concentration calculated. The Pco_2 is 7-8 mm Hg higher and the pH 0.03-0.04 unit lower in venous than arterial plasma because venous blood contains the CO_2 being carried from the tissues to the lungs. Therefore, the calculated HCO_3^- concentration is about 2 mmol/L higher. However, if this is kept in mind, free-flowing venous blood can be substituted for arterial blood in most clinical situations.

A measurement that is of some value in the differential diagnosis of metabolic acidosis is the **anion gap**. This gap which is something of a misnomer, refers to the difference between the concentration of cations other than Na^+ and the concentration of anions other than Cl^- and HCO_3^- in the plasma. It consists for the most part of proteins in the anionic form, HPO_4^{2-}, SO_4^{2-}, and organic acids, and a normal value is about 12 meq/L. It is increased when the plasma concentration of K^+, Ca^{2+}, or $Mg2+$ is decreased; when the concentration of or the charge on plasma proteins is increased; or when organic anions such as lactate or foreign anions accumulate in blood. It is decreased when cations are increased or when plasma albumin is decreased. The anion gap is increased in metabolic acidosis due to ketoacidosis, lactic acidosis, and other forms of acidosis in which organic anions are increased. It is not increased in hyperchloremic acidosis due to ingestion of NH_4CI or carbonic anhydrase inhibitors.

(Ref. Ganong 22th Edition; Page 736)

N.B.

Plasma anion gap :

Law of neutrality : Cations = Anions

i.e $Na^+ + K^+$ + unmeasured cations (UC)

$= Cl^- + HCO_3^-$ + unmeasured anions (UA)

$(Na^+ + K^+) - (Cl^- + HCO_3^-)$

= Unmeasured anions - unmeasured cations

= UA - UC

= Anion gap

UC : Ca++, Mg++, gama globulin

UA : Plasma protein, SO_4, PO_4, lactate, others

Normal value : 12 (+/-) 4 meq/L.

Causes of increased anion gap :

i. Renal failure

ii. Lactic acidosis

iii. Ketoacidosis

iv. Intoxication of aspirin, alcohol poisoning.

N.B. End product of alcohol metabolism → organic acid → anion of that organic acid → increase anion gap).

Plasma pH, HCO_3^-, and P_{CO_2} values in varios typical disturbances of acid base balance : *(Arterial plasma)*

Condition	*pH*	*HCO_3^- (meq/L)*	*P_{CO_2} (mmHg)*	*Cause*
Normal	7.40	24.1	40	
Metabolic	*7.28*	*18.1*	*40*	*NH_4Cl ingestion*
acidosis	*6.96*	*5.0*	*23*	*Diabetic acidosis*
Metabolic	7.50	30.1	40	$NaHCO_3$ ingestion
alkalosis	7.56	49.8	58	Prolonged vomitting
Respiratory	*7.34*	*25.0*	*48*	*Breathing 7% CO_2*
acidosis	*7.34*	*33.5*	*64*	*Emphysema*
Respiratory	7.53	22.0	27	Voluntary hyperventilation
alkalosis	7.48	18.7	26	Three-week residence at 4000-maltitude

(Ref. Ganong 22th Edition; Page 736)

Acid base disorder

Types of acid base disorder :

1. *Simple acid base disorder* :
   - i. *Metabolic*
     - a. Acidosis (decrease HCO_3^-)
     - b. Alkalosis (increase HCO_3^-)
   - ii. *Respiratory*
     - a. Acidosis (increase PCO_2)
     - b. Alkalosis (decrease PCO_2)
2. *Complex acid base disorder* : If both component vary. Any combination of 4 simple acid base disorder, but all four can not persist in a body.

Acid base parameters

1. Classical acid base parameters
   - i. pH (7.4)
   - ii. PCO_2 (40 mm of Hg)
2. Non classical acid base parameters
   - i. Plasma anion gap
   - ii. Electrolytes.

Respiratory Acidosis

A rise in arterial P_{CO_2} due to decreased ventilation causes *respiratory acidosis*. The CO_2 that is retained is in equilibrium with H_2CO_3, which in turn is in equilibrium with HCO_3^-, so that the plasma HCO_3^- rises and a new equilibrium is reached at a lower pH.

Conversely, a decline in P_{CO_2} causes *respiratory alkalosis*.

(Ref. Ganong 22th Edition; Page-734)

Causes of respiratory acidosis :

i. Physiological :
   a. Alveolar hypoventilation.
   b. Increased CO_2 in atmosphere.

ii. Pathological :
   a. Chronic obstructive pulmonary disease (COPD)
   b. Asthma, pneumonia, emphysema, chronic bronchitis
   c. Poliomyelitis
   d. Neuromuscular causes
   e. Chest deformities- kyphosis, iordosis etc
   f. Depression of respiratory centre- morphine poisoning.

Renal compensation of respiratory acidosis : HCO_3^- reabsorption in the renal tubules depends not only on the filtered load of HCO_3^-, which is the product of the GFR and the plasma HCO_3^- level, but also on the rate of H^+ secretion by the renal tubular cells, since HCO_3^- is reabsorbed by exchange for H^+. The rate of H^+ secretion and hence the rate of HCO_3^- reabsorption is proportionate to the arterial P_{CO_2}, probably because the more CO_2 that is available to form H_2CO_3 in the cells, the more H^+ can be secreted. Furthermore, when the P_{CO_2} is high, the interior of most cells becomes more acidic.

In respiratory acidosis, renal tubular H^+ secretion is therefore increased, removing H^+ from the body; and even though the plasma HCO_3^- is elevated, HCO_3^- reabsorption is increased, further raising the plasma HCO_3^-. Cl^- excretion is increased, and plasma Cl^- falls as plasma HCO_3^- is increased.

(Ref. Ganong 22th Edition; Page-734)

In respiratory acidosis :

$$= \frac{HCO_3^-}{\textit{increased } PCO_2}$$

$$\textit{Compensation} = \frac{\text{increase } HCO_3^-}{\text{increased } PCO_2}$$

→ pH becomes normal, but total body CO_2 increases due to * *HCO_3^- generation* by the kidney *(Kidney system managed).*

Respiratory Alkalosis

A decline in P_{CO_2} causes *respiratory alkalosis.*

Causes of respiratory alkalosis :

a. Hyperventilation
b. Hysteria
c. Hyperapnoea at high altitude

d. Salicylate poisoning
e. Lobar pneumonia
f. Meningitis
g. Enchephalitis
h. Hepatic failure.

Renal compensation in respiratory alkalosis, the low P_{CO_2} hinders renal H^+ secretion, HCO_3^- reabsorption is depressed, and HCO_3^- is excreted, further reducing the already law plasma HCO_3^- and lowering the pH towards normal.

(Ref. Ganong 22th Edition; Page-734)

Respiratory alkalosis :

$$= \frac{HCO_3^-}{\textit{decreased } PCO_2}$$

$$\textit{Compensation} = \frac{\text{decrease } HCO_3^-}{\text{decreased } PCO_2}$$

→ pH becomes normal,
but total body CO_2 decreases due to * *increase HCO_3^- excretion* by the kidney
(Kidney sysrem managed).

Metabolic acidosis

When acids stronger than HHb and the other buffer acids are added to blood, *metabolic acidosis* is produced. If, for example, H_2SO_4 is added, the H^+ is buffered and the Hb^-, $Prot^-$, and HCO_3^- levels in plasma drop. The H_2CO_3 formed is converted to H_2O and CO_2, and the CO_2 is rapidly excreted via the lungs. This is the situation in uncompensated metabolic acidosis. Actually, the rise in plasma H^+ stimulates respiration, so that the P_{CO_2}, instead of rising or remaining constant, is reduced. This *respiratory compensation* raises the pH even further.

(Ref. Ganong 22th Edition, Page 734)

Causes :

a. Diarrhea
b. Diabetic mellitus
c. Renal failure (failure of excretion of metabolic acid)
d. Ingestion of acids
e. Formation of excessive quantities of metabolic acid in the body
f. Loss of excessive alkali from the body
g. Intravenous administration of metaoolic acid
h. Acidic poisoning i.e acetyl salicylates (aspirin) and methyl alcohol.

Renal compensation : The *renal compensatory* mechanisms then bring about the excretion of the extra H^+ and return the buffer systems to normal.

The anions that replace HCO_3^- in the plasma in metabolic acidosis are filtered, each with a cation (principally Na^+), thus maintaining electrical neutrality. The renal tubular cells secrete H^+ into the tubular fluid in exchange for Na^+; and for each H^+ secreted, one Na^+ and one HCO_3^- are added to the blood. The limiting urinary pH of 4.5 would be reached rapidly and the total amount of H^+ secreted would be small if there were no buffers in the urine that tied up H^+. However secreted H^+ reacts with HCO_3 to form CO_2 and H_2O (bicarbonate reabsorption); with HPO_4^{2-} to form $H_2PO_4^-$ and with NH_3 to form NH_4^+. In this way large amounts of H^+ can be secreted, permitting correspondingly large amounts of HCO_3^- to be returned to (in the case of bicarbonate reabsorption) or added to the depleted body stores and large numbers of the cations to be reabsorbed. It is only when the acid load is very large that cations are lost with the anions, producing diuresis and depletion of body cation stores. In chronic acidosis, glutamine synthesis in the liver is increased, using some of the NH_4^+ that usually is converted to urea, and the glutamine provides the kidneys with an additional source of NH_4^+. NH_3 secretion increases over a period of days, further improving the renal compensation for acidosis. In addition, the metabolism of glutamine in the kidneys produces alpha-ketoglutarate, and this in turn is decarboxylated, producing HCO_3^- which enters the bloodstream and helps buffer the acid load.

Metabolic acidosis :

$$= \frac{\textit{decreased } HCO_3^-}{PCO_2}$$

$$\textit{Compensation} = \frac{\text{decreased } HCO_3^-}{\text{decrease } PCO_2}$$

→ pH becomes normal,
but total body CO_2 decreases due to * *hyperventilation*
(Respiratory sysrem managed).

The overall reaction in blood when a strong acid such as H_2SO_4 is added is

$$2NaHCO_3 + H_2SO_4 \qquad Na_2SO_4 + 2H_2CO_3$$

For each mole of H^+ added, 1 mole of $NaHCO_3$ is lost. The kidney in effect reverses the reaction :

$$Na_2SO_4 + 2H_2CO_3 \qquad 2NaHCO_3 + 2H^+ + SO_4^{2-}$$

and the H^+ and SO_4^{2-} are excreted. Of course, H_2SO_4 is not excreted as such, the H^+ appearing in the urine as titratable acidity and NH_4^+.

In *metabolic acidosis*, the respiratory compensation tends to inhibit the renal response in the sense that the induced drop in P_{CO_2}, hinders acid secretion, but it also decreases the filtered load of HCO_3^- and so its net inhibitory effect is not great.

(Ref. Ganong 22th Edition, Page 734, 735)

Metabolic Alkalosis

When the free H^+ level falls as a result of addition of alkali or removal of acid, *metabolic alkalosis* results. In metabolic alkalosis, the plasma HCO_3^- level and pH rise.

Causes :

a. Administration of diuretics
b. Excess aldosterone secretion
c. Vomiting of gastric contents- rich in HCI
d. Ingestion of alkaline drugs i.e $NaHCO_3$ for gastritis or peptic ulcer.

Respiratory compensation : The respiratory compensation is a decrease in ventilation produced by the decline in H^+ concentration, and this elevates the Pco_2. This brings the pH back toward normal while elevating the plasma HCO_3^- level still further. The magnitude of this compensation is limited by the carotid and aortic chemoreceptor mechanisms, which drive the respiratory center if there is any appreciable fall in the arterial Po_2. In metabolic alkalosis, more renal H^+ secretion is expended in reabsorbing the increased filtered load of HCO_3^- and if the HCO_3^- level in plasma exceeds 26-28 meq/L, HCO_3^- appears in the urine. The rise in Pco_2 inhibits the renal compensation by facilitating acid secretion, but its effect is relatively slight.

(Ref. Ganong 22th Edition, Page 735)

Metabolic alkalosis :

$$= \frac{\textit{increased } HCO_3^-}{PCO_2}$$

$$\text{Compensation} = \frac{\text{increased } HCO_3^-}{\text{increase } PCO_2}$$

→ pH becomes normal,
but total body CO_2 increases due to * *hypoventilation*
(Respiratory sysrem managed).

Q.03. **Define alkalosis? Classify it. What is the effects of alkalosis on the body.**

i. *Definition* : It may be defined as a pathological condition in which H^+ is decreased below 43.6 rnEq/L of blood or pH is increased above 7.4 due to the accumulation of base or the loss of acid in the body.

ii. *Types* :

a. Respiratory alkalosis : A decreased arterial PCO_2 below normal resulting in increase pH is called respiratory alkalosis.

b. Metabolic alkalosis : An increased pH due to increase HCO_3^- concentration is called metabolic alkalosis.

iii. *Effects* :

a. Over excitation of nervous system.

b. Muscles go into a state of tetany i.e a state of tonic spasm.

c. Tetany usually appears first in the muscles of forearm, then spreads rapidly to the muscles of the face and finally all over the body.

d. Extremely alkaline patients may die for tetany of respiratory muscles.

(Q. Write short notes on- Alkalosis)

In compensatory mechenism of acid baes disorder :

4 sequele occurs :

1. Total body CO_2 decreases in-
   i. Metabolic acidosis
   ii. Respiratory alkalosis
   iii. Metabolic acidosis + Respiratory alkalosis.
2. Total body CO_2 increases in-
   i. Metabolic alkalosis
   ii. Respiratory acidosis.
3. Total body CO_2 normal with acid baes disorder in-
   i. Metabolic acidosis + Respiratory acidosis
   ii. Metabolic alkalosis + Respiratory alkalosis.
4. Total body CO_2 normal with acid baes disorder in-
   i. Metabolic acidosis + Metabolic alkalosis.

Q.00. **Define acidosis. Classify it.**

i. *Definition* : It may be defined as a pathological condition in which H^+ is increased above 43.6 mEq/L of blood or pH is decreased below 7.4 due to accumulation of acid or loss of base in the body.

ii. *Types* :

a. Respiratory acidosis : An increased arterial PCO_2 above normal resulting in decrease pH is called respiratory acidosis.

b. Metabolic acidosis : Decreased pH due to HCO_3^- deficit is called metabolic acidosis.

Q.02. **What is the effects of acidosis on the body?**

Ans. Effects of acidosis : The major effect of acidosis is depression of the CNS. The nervous system becomes so depressed that the person becomes disoriented and latter comatose. Therefore patients dying of diabetic acidosis, uraemic acidosis and other types of actdosis usually die in state of coma.

(Q: Write short notes on-Acidosis. Ans. Definition + Types + Effects on body)

Renal handling of various plasma constituents in a normal adult human on an average diet.

Substance	Per 24 Hours				Percentage Reabsorbed	Location
	Filtered	Reabsorbed	Secreted	Excreted		
Na^+ (meq)	26,000	25,850		150	99.4	P, L, D, C
K^+ (meq)	600	560[2]	50[2]	90	93.3	P, L, D, C
Cl^- (meq)	18,000	17,850		150	99.2	P, L, D, C
HCO_3^-(meq)	4,900	4,900		0	100	P, D
Urea (mmol)	870	460[3]		410	53	P, L, D, C
Creatinine (mmol)	12	1[4]	1[4]	12		
Uric acid (mmol)	50	49	4	5	98	P
Glucose (mmol)	800	800		0	100	P
Total solute (mosm)	54,000	53400	100	700	87	P, L, D, C
Water (mL)	180,000	179,000		1000	99.4	P, L, D, C

[1] *P, proximal tubules; L, loops of Henle; D, distal tubules; C, collecting ducts.* [2] *K^+ is both reabsorbed and secreted.*
[3] *Urea diffuses into as well as out of some portions of the nephron.*
[4] *Variable secretion and probable reabsorption of creatinine in humans.*

(Ref. Ganong 22th Edition, Page 710)

Urine

Mechanism of formation of urine

Urine formation takes place by the following three mechanism.

i. Formation of glomerular filtrate.
ii. Reabsorption of glomerular filtrate from tubule.
iii. Tubular secretion.

Formation of glomerular filtrate : Due to the effective filtration pressure glomerular filtrate is formed through the glomerular membrane. Total amount of glomerular filtrate is 180 liter/ day.

Tubular reabsorption : Please see page 13.24

Tubular secretion :

a. *In proximal tubule :* H^+, K^+& NH_3 is secreted.
b. *In thin segment :* Na^+ by the passive diffusion .
c. *In thick segment :* Urea by passive diffusion.
d. *In distal tubule :* NH_3 is secreted and also K^+ & H^+ with the help of exchange pump.

In these way urine is formed.

Mechanism of formation of dilute urine

When the glomerular filtrate is initially formed, its osmolarity is about the same as plasma (300 mOsm/L). To excrete excess water, it is necessary to dilute the fiirate as it passes along the tubule. This is achieved by reabsorbing solutes to a greater extent than water.

i. *Tubular fluid remains isosmotic in the proximal tubule* : As fluid flows through the proximal tubule, solutes and water are reabsorbed in equal proportions, so that little change in osmolarity occurs; that is, the proximal tubule fluid remains isosmotic to the plasma, with an osmolarity of about 300 mOsm/L.

ii. As fluid passes down the *descending loop of Henle*, water is reabsorbed by osmosis and the tubular fluid reaches equilibrium with the surrounding interstitial fluid of the renal medulla, which is very hypertonic- about two to four times the osmolarity of the original glomerular filtrate. Therefore, the *tubular fluid becomes more concentrated as it flows into the inner medulla.*

iii. *Tubular fluid becomes dilute in the ascending loop of Henle* : In the ascending limb of the loop of Henle, especially in the thick segment, sodium, potassium, and chloride are avidly reabsorbed. However, this portion of the tubular segment is impermeable to water, even in the presence of large amounts of ADH. Therefore, the tubular fluid becomes more dilute as it flows up the ascending loop of Henle into the early distal tubule, with the *osmolarity decreasing progressively to about 100 mOsm/L* by the time the fluid enters the early distal tubular segment. Thus, *regardless of whether ADH is present or absent, fluid leaving the early distal tubular segment is hypo-osmotic, with an osmolarity of only about one third the osmolarity of plasma.*

iv. *Tubular fluid in the distal and collecting tubules is further diluted in the absence of ADH* : As the dilute fluid in the

early distal tubule passes into the late distal convoluted tubule, cortical collecting duct, and collecting duct, there is additional reabsorption of sodium chloride. *In the absence of ADH, this portion of the tubule is also impermeable to water, and the additional reabsorption of solutes causes the tubular fluid to become even more dilute, decreasing its osmolarity to as low as 50 mOsm/L.* The failure to reabsorb water and the continued reabsorption of solutes lead to a large volume of dilute urine.

N.B. To summarize, *the mechanism for forming a dilute urine* is to continue reabsorbing solutes from the distal segments of the tubular system while failing to reabsorb water. In healthy kidneys, *fluid leaving the ascending loop of Henle and early distal tubule is always dilute, regardless of the level of ADH.* In the *absense of ADH, the urine is further diluted in the late distal tubule and collecting ducts*, and a large volume of dilute urine is excreted.

(Ref. Guyton & Hall 11th Edition; Page 348, 349)

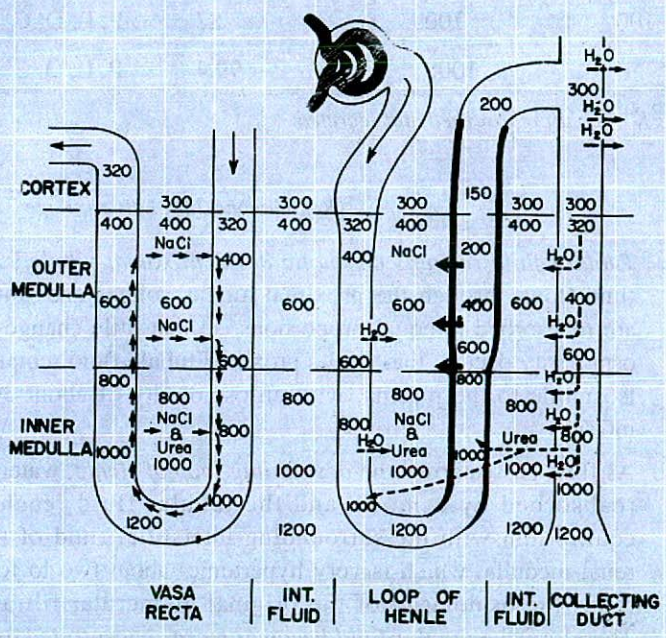


Fig. 13-7 . The countercurent mechanism for concentrating the urine (numerical value are in milliosmoles per liter)

Counter current hypothesis : A small change of osmolarity at any level of fluid flowing in counter direction in the two parallel tubules connected each other in hair pin manner can be multiplied several times along the length of the tubules.

Counter current mechanism

When a fluid passes through two parallel stem of 'U' shaped tube in opposite direction with close proximity is called counter current mechanism . During this counter current flow tremendous concentration of solute can be build up at the top of the loop.

U shaped vasa recta is called the counter current exchanger.
U shaped loop of Henle is called counter current multiplier.

Counter current exchange mechanism

There are two special features of the renal medullary blood flow that contribute to the preservation of the high solute concentrations:

i. *The medullary blood flow is low*, accounting for only 1 to 2 per cent of the total renal blood flow. This sluggish blood flow is sufficient to supply the metabolic needs of the tissues but helps to minimize solute loss from the medullary interstitium.

ii. *The vasa recta serve as countercurrent exchangers*, minimizing washout of solutes from the medullary interstitium.

The countercurrent exchange mechanism operates as follows :
Blood enters and leaves the medulla by way of the vasa recta at the boundary of the cortex and renal medulla. The vasa recta, like other capillaries, are highly permeable to solutes in the blood, except for the plasma proteins. As blood descends into the medulla toward the papillae, it becomes progressively more concentrated, partly by solute entry from the interstitium and partly by loss of water into the interstitium. By the time the blood reaches the tips of the vasa recta, it has a concentration of about 1200 mOsm/L, the same as that of the medullary interstitium. As blood ascends back toward the cortex, it becomes progressively less concentrated as solutes diffuse back out into the medullary interstitium and as water moves into the vasa recta.

Thus, although there is a large amount of fluid and solute exchange across the vasa recta, there is little net dilution of the concentration of the interstitial fluid at each level of the renal medulla because of the U shape of the vasa recta capillaries, which *act as countercurrent exchangers*. Thus, *the vasa recta do not create the medullary hyperosmolarity, but they do prevent it from being dissipated.*

Function : Thus, under steady-state conditions, the vasa recta carry away only as much solute and water as is absorbed from the medullary tubules, and *the high concentration of solutes established by the countercurrent mechanism is maintained.*

(Ref.Guyton & Hall 11th Edition; Page 354)

Counter current multiplier mechanism

Definition : The repetitive reabsorption of sodium chloride by the thick ascending loop of Henle and continued inflow of new sodium chloride from the proximal tubule into the loop of Henle is called the *countercurrent multiplier*.

The sodium chloride reabsorbed from the ascending loop of Henle keeps adding to the newly arrived sodium chloride, thus *'multiplying' its concentration in the medullary interstitium.*

Steps involved in causing the hyperosmotic renal medullary interstitium :

First, assume that the loop of Henle is filled with fluid with a

concentration of 300 mOsm/L, the same as that leaving the proximal tubule.

Step 2 : Next, the active pump of the thick ascending limb on the loop of Henle is turned on, reducing the concentration inside the tubule and raising the interstitial concentration; this pump establishes a 200-mOsm/L concentration gradient between the tubular fluid and the interstitial fluid (*step 2*). The limit to the gradient is about 200 mOsm/L because paracellular diffusion of ions back into the tubule eventually counterbalances transport of ions out of the lumen when the 200-mOsm/L concentration gradient is achieved.

Step 3 is that the tubular fluid in the descending limb of the loop of Henle and the interstitial fluid quickly reach osmotic equilibrium because of osmosis of water out of the descending limb. The interstitial osmolarity is maintained at 400 mOsm/L because of continued transport of ions out of the thick ascending loop of Henle. Thus, by itself, the active transport of sodium chloride out of the thick ascending limb is capable of establishing only a 200-mOsm/L concentration gradient, much less than that achieved by the countercurrent system.

Step 4 is additional flow of fluid into the loop of Henle from the proximal tubule, which causes the hyperosmotic fluid previously formed in the descending limb to flow into the ascending limb. Once this fluid is in the ascending limb, additional ions are pumped into the interstitium, with water remaining behind, until a 200-mOsm/L osmotic gradient is established, with the interstitial fluid osmolarity rising to 500 mOsm/L *(step 5)*. Then, once again, the fluid in the descending limb reaches equilibrium with the hyperosmotic medullary interstitial fluid *(step 6)*, and as the hyperosmotic tubular fluid from the descending limb of the loop of Henle flows into the ascending limb, still more solute is continuously pumped out of the tubules and deposited into the inedullary interstitium.

These steps are repeated over and over, with the net effect of adding more and more solute to the medulla in excess of water, with sufficient time, *this process gradually traps solutes in the medulla and multiplies the concentration gradient established by the active pumping of ions out of the thick ascending loop of Henle, eventually raising the interstitial third osmolarity to 1200 to 1400 mOsm/L.*

(Ref. Guyton & Hall 11th Edition; Page 351)

Concentrated urine

Mechanism of formation of concentrated urine : The ability of the kidney to form a urine that is more concentrated than plasma is essential for survival of mammals that live on land, including humans. The basic requirements for forming a concentrated urine are-

1. *A high level of ADH*, which increases the permeability of the distal tubules and collecting ducts to water, thereby allowing these tubular segments to avidly reabsorb water.
2. *A high osmolarity of the renal medullary interstitial fluid*, which provides the osmotic gradient necessary for water reabsorption to occur in the presence of high levels of ADH.

   The major factors that contribute to the buildup of solute concentration into the renal medulla are as follows :

   i. Active transport of sodium ions and co-transport of potassium, chloride, and other ions out of the thick portion of the ascending limb of the loop of Henle into the medullary interstitium.

   ii. Active transport of ions from the collecting ducts into the medullary interstitium.

   iii. Passive diffusion of large amounts of urea from the inner medullary collecting ducts into the medullary interstitium.

   iv. Diffusion of only small amounts of water from the medullary tubules into the medullary interstitium, far less than the reabsorption of solutes into the medullary interstitium

(Ref. Guyton & Hall 11th Edition; Page 350, 351)

Acidification of urine

The ability of the renal tubules to reduce urinary pH is called acidification of urine. The major sites of urine acidification are the distal and collecting tubules. Acidification of urine requires following processes :

i. *H^+ secretion in the tubular fluid* : H^+ that are secreted into tubular fluid is generated by metabolism. Approximately 4300 mEq H^+ is secreted daily. Since the lowest pH attainable in urine is 4.5 i.e H^+ is $40x10^{-6}$ Eq/L and the plasma H^+ is $40x10^{-9}$ Eq/L., kidney can cause a 1000 fold H^+ gradient between plasma and urine. The majority of secreted H^+ is used to bring about HCO_3^- reabsorption, and therefore is not excreted. Only 50-70 mEq is excreted daily.

ii. *Bicarbonate buffering* i.e. reabsorption of filtered HCO_3^- : The filtered HCO_3^- is reabsorbed in the form of CO_2 from the tubular lumen. The CO_2 returns to the tubular cell to form another H^+ ($CO_2 + H_2O \quad H_2CO_3 \quad H^+ + HCO_3^-$) and therefore no net H^+ secretion occurs. For each mole of HCO_3^- removed from the tubular fluid, 1 mol of HCO_3^- diffuses from the tubular cells into the blood. HCO_3^- absorption does not contribute urinary excretion of acid.

iii. *Non-bicarbonate buffering* i.e. formation of titratable acid and NH_4^+.

Physical characteristics of normal urine

i.	Appearance	: Straw or yellow amber
ii.	Smell	: Paint aromatic
iii.	Volume	: 800-2500 ml

iv. Specific gravity : 1015-1030
v. Osmolality : 800-1200 mosm/L
vi. pH : 4.5-8.0 (average 6.0).

Composition of urine :

i. *The normal daily constituents of urine* :

Constituents	*Amount (average)*
a. H_2O	: 1.2 liters
b. Na^+	: 150-200 mmol
c. K^+	: 90-100 ml
d. Cl^-	: 100-150 ml
e. HCO_3^-	: 2-3 mmol
f. Urea	: 410 mmol
g. Uric acid	: 5 mmol
h. Creatinine	: 12-15 mmol
i. Foreign substances	: Variable amount

ii. *In additian to these substances the normal urine contains* :

a. Glucose	: No
b. Protein	: 150-200 mg daily
c. Albumin	: <20 mg/litre urine
d. RBC	: No red blood cells (the presence of single RBC is abnormal)
e. WBC	: 0-2 per cubic millimeter of urine
f. Casts	: hyaline or granular.

Applied

Anuria : The presence of no urine in 24 hours is called anuria. It suggests urinary tract obstruction until proved otherwise.

Oliguria : Oliguria usually defined as the excretion of less than 300 ml of urine per day.

Causes :
a. Hypovolaenia
b. Cardiac failure
c. Septicaemia
d. Acute glomerulonephritis
e. Acute tubular necrosis

Polyuria : Polyuria is a persistent, large increase in urine output usually associated with nocturia.

Causes :
a. Excessive intake of water
b. Increased osmotic load as in hyperglycaemia and glycosunia.
c. Defective renal concentrating ability or failure of production of ADH

Proteinuria : The presence of protein in the urine, which is detectable by dipstrix, (usually > 200 mg daily) is called proteinuria.

Common causes :
a. Pyrexia
b. Exercise
c. Nephrotic syndrome (>3 gm/day)
d. Acute glomerulonephritis
e. Multiple myeloma
f. Diabetic nephropathy.

Glycosuria : The presence of glucose in urine is called glycosuria. The normal urine contains no glucose.

Causes :
a. Diabetes mellitus
b. Pregnancy : due to fall in the renal threshold for glucose.
c. Alimentary glycosuria.

Haematuria : The presence of blood in the urine is called haeinaturia. The urine appears smoky, brighl red or reddish brown.

Causes :
a. Glornerulonephritis
b. Pyelonephritis
c. Hypoplasia of kidney and bladder
d. Stone in the urinary tract
e. Trauma
f. Cystitis.

Micturition

Anatomic considerations : The smooth muscle of the bladder, like that of the ureters, is arranged in spiral, longitudinal, and circular bundles. Contraction of this muscle, which is called the detrusor muscle, is mainly responsible for emptying the bladder during urination (micturition). Muscle bundles pass on either side of the urethra, and these fibers are sometimes called the *internal urethral sphincter*, although they do not encircle the urethra. Farther along the urethra is a sphincter of skeletal muscle, the sphincter of the *membranous urethra (external urethral sphincter)*. The bladder epithelium is made up of a superficial layer of flat cells and a deep layer of cuboidal cells.

(Ref. Ganong 22th Edition)

Innervation of the urinary bladder

The principal nerve supply of the bladder is by way of the *pelvic nerves*, which connect with the spinal cord through the *sacral plexus*, mainly connecting with cord segments S-2 and S-3. Coursing through the pelvic nerves are both *sensory nerve fibers* and *motor nerve fibers*.

The *sensory fibers detect* the degree of stretch in the bladder wall. Stretch signals from the posterior urethra are especially strong and are mainly responsible for initiating the reflexes that cause bladder emptying.

The *motor nerves* transmitted in the pelvic nerves are

parasympathetic fibers. These terminate on ganglion cells located in the wall of the bladder. Short postganglionic nerves then innervate the detrusor muscle.

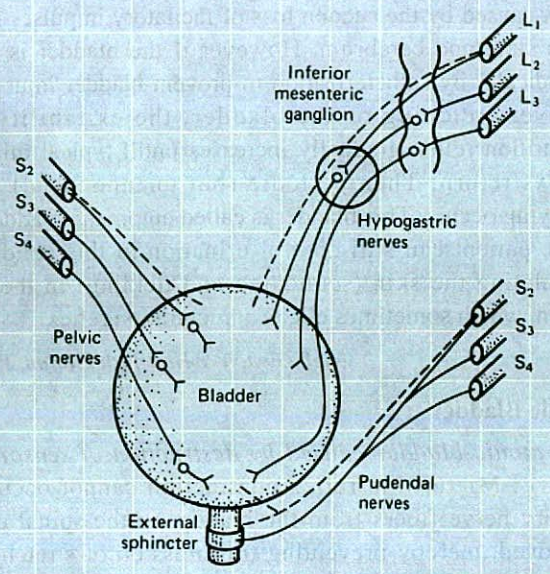


Fig. 13-8.Innervation of the bladder. Dashed lines indicate sensory nerves. Parasympathetic innervation is shown at the left, sympathetic at the upper right, and somatic at the lower right.

In addition to the pelvic nerves, two other types of innervation are important in bladder function. Most important are the *skeletal motor fibers* transmitted through the *pudendal nerve to the external bladder sphincter.* These are *somatic nerve fibers* that innervate and control the voluntary skeletal muscle of the sphincter. Also, the bladder receives *sympathetic innervation* from the sympathetic chain through the hypogastric nerves, connecting mainly with the L-2 segment of the spinal cord. These sympathetic fibers stimulate mainly the blood vessels and have little to do with bladder contraction. Some sensory nerve fibers also pass by way of the sympathetic nerves and may be important in the sensations of fullness and, in some instances, pain.

(Ref. Guyton & Hall 11th Edition, Page 312)

Micturition : Micturition is fundamentally a spinal reflex facilitated and inhibited by higher brain centers and, like defecation, *subject to voluntary facilitation and inhibition.* Urine enters the bladder without producing much increase in intravesical pressure until the viscus is well filled. In addition, like other types of smooth muscle, the bladder muscle has the property of plasticity; when it is stretched, the tension initially produced is not maintained.

(Ref. Ganong 22th Edition, Page 726

Micturation reflex

Mticturition contractions are the result of a stretch reflex initiated by *sensory stretch receptors* in the bladder wall, especially by the receptors in the posterior urethra when this area begins to fill with urine at the higher bladder pressures. Sensory signals from the bladder stretch receptors are conducted to the sacral segments of the cord through the pelvic nerves and then reflexively back again to the bladder through the *parasympathe tic nerve* fibers by way of these same nerves.

When the bladder is only partially filled, these micturition contractions usually relax sponta- neously after a fraction of a minute, the detrusor muscles stop contracting, and pressure falls back to the baseline. As the bladder continues to fill, the rnicturition reflexes become more frequent and cause greater contractions of the detrusor muscle.

Once a micturition reflex begins, it is 'self-regenerative'. That is, initial contraction of the bladder further activates the stretch receptors to cause still further increase in sensory impulses to the bladder and posterior urethra, which causes further increase in reflex contractiwn of the bladder; thus, the cycle is repeated again and again until the bladder has reached a strong degree of contraction. Then, after a few seconds to more than a minute, the self-regenerative reflex begins to fatigue and the regenerative cycle of the micturition reflex ceases, permitting the bladder to relax.

Thus, *the micturition reflex is a single complete cycle of-* i. *progressive and rapid increase of pressure.* ii. *a period of sustained pressure* and iii. *return of the pressure to the basal toneof the bladder.* Once a micturition reflex has occurred but has not succeeded in emptying the bladder, the nervous elements of this reflex usually remain in an inhibited state for a few minutes to 1 hour or more before another micturition reflex occurs. As the bladder becomes more and more filled, micturition reflex occur more and more often and more and more powerfully.

Once the micturition reflex becomes powerful enough, causes another reflex, which passes through the *pudendal nerves* to the external sphincter to inhibit it. If this inhibition is more potent in the brain than the voluntary constrictor signals to the external sphincter, urination will occur. If not, urination will not occur until the bladder fills still further and the micturition reflex becomes more powerful.

(Ref. Guyton & Hall 11th Edition, Page 313)

Facilitation or inhibition of micturition by the brain

The micturition reflex is a completely autonomic spinal cord reflex. but it can be inhibited or facilitated by centers in the brain. These centers include- i. *strong facilitorv and inhibitory centers in the brain stem, located mainly in the pons*, and ii. *several centers, located in the cerebral contex* that are mainly inhibitory but can become excitatory.

The micturition reflex is the basic cause of micturition. but the higher centers normally exert final control of micturition as follows :

1. The higher centers keep the micturition reflex partially inhibited except when micturition is desired.

2. The higher centers can prevent micturition; even if the micturition reflex does occur, by continual tonic contraction of the external bladder sphincter until a convenient time presents itself.
3. When it is time to urinate, the cortical centers can facilitate the sacral micturition centers to help initiate a micturition reflex and at the same time inhibit the external urinary sphincter so that urination can occur.

Voluntary urination is usually initiated in the following way : *First*, a person voluntarily contracts his or her abdominal muscles, which increases the pressure in the bladder and allows extra urine to enter the bladder neck and posterior urethra under pressure, thus stretching their walls. This stimulates the stretch receptors, which excites the micturition reflex and simultaneo-usly inhibits the external urethral sphincter. *Ordinarily, all the urine will be emptied, with rarely more than 5 to 10 milliliters left in the bladder.*

(Ref. Guyton & Hall 11th Edition, Page 313)

Stages of micturation

a. Set up of micturation reflex due to accumulation of urine into urinary bladder.
b. Relaxation of perineal muscle except sphincter urethrae.
c. Contraction of muscles of abdominal wall.
d. Firm contraction of detrusor muscle and relaxation of sphincter vesicae.
e. Ultimately relaxation of sphincter of urethrae due to flow of urine as a result of relaxation of sphincter vesicae.
f. Bladder become empty by the contraction of detrusor muscle and muscle of the abdominal wall.
g. As act is completed, the reversal phenomena happens.

Some conditions

Aneurea	:	Cessation of urine flow due to sever kidney disease.
Oligurea	:	Marked reduction of urinary output is called oligurea.
Polyurea	:	Increased in urinary output is called polyurea.
Glucosurea	:	Presence of glucose in urine.
Albuminurea	:	Presence of Albumin in urine.
Proteinurea	:	Presence of abnormal quantity of protein in urine.
Haematurea	:	Presence of blood in urine.
Nocturea	:	Passage of more urine at night.
Ketonurea	:	Presence of keton bodies in urine.

Automatic bladder

If the spinal cord is damaged above the sacral region but the sacral segments are still intact, typical micturation reflexs can still occur. However, they are no longer controlable by the brain. During the first few days to several weeks after the damage to the cord has occured, the micturation reflexes are completely suppressed because of of the state of state of *spinal shock* caused by the sudden loss of facilatory impulses from the brain stem and cerebrum. However if the bladder is emptied periodically by catheterization to prevent bladder injury caused by overstretching of the bladder, the exitability of the micturition reflex gradually increases untill typical micturition reflexs return; Then periodic (but unannounced) bladder emptying occurs. This bladder is called automatic bladder.

Some patient can still control urination in this condition by stimulating the skin (scratching and tickling) in the genital region, which sometimes elicits a micturation reflex.

(Ref. Guyton & Hall 11th Edition, Page 314)

Atonic Bladder

(The atonic bladder caused by destruction of sensory nerve fibers) : Micturition reflex contraction cannot occur if the sensory nerve fibers from the bladder to the spinal cord are destroyed, thereby preventing transmission of stretch signals from the bladder. When this happens, a person loses bladder control, despite intact efferent fibers from the cord to the bladder and despite intact neurogenic connections within the brain. Instead of emptying periodically, the bladder fills to capacity and overflows a few drops at a time through the urethra. This is called *overflow incontinence.*

A *common cause of atonic bladder* is crush injury to the sacral region of the spinal cord. Certain diseases can also cause damage to the dorsal root nerve fibers that enter the spinal cord. For example, syphilis can cause constrictive fibrosis around the dorsal root nerve fibers, destroying these fibers. This condition is called *tobes dorsalis*, and the resulting bladder condition is called *tabetic bladder.*

(Ref. Guyton & Hall 11th Edition, Page 313)

Un-inhibited Neurogenic Bladder

It results in frequent and relatively uncontrolable micturation. This condition is drives from the partial damage in the spinal cord or the brain stem that interrupts most of the inhibitory signals. Therefore, facilitatory impulses passsing continually down the cord keep the sacral centers so excitable that even a small quantity of urine will elicit an uncontrollable micturition reflex, and thereby promote frequent urination.

(Ref. Guyton & Hall 11th Edition, Page 314)

Abnormalities of micturation

Disorders of micturation may results from neural lesions. The pattern of neurogenic bladder dysfunction are :

i. Atonic bladder with overflow incontinence.
ii. Hypertonic bladder with urge incontinence
iii. Abnormality due to cortical lesions.

Lower motor neuron lesions- LMNL : It causes a flaccid, atonic bladder, which overflows without warning. It must be bilateral to cause urinary symptoms.

Bilateral upper motor neuron lesions (UMNL) : It causes frequency of micturation and incontinence. The bladder is small and usually sensitive to small change in intravesicle pressure.

Effects of deafferentation : When the sacral dorsal roots are cut in experimental animals or interrupted by diseases of the dorsal roots such as *tabes dorsalis* in humans, all reflex contractions of the bladder are abolished. The bladder becomes distended, thin-walled, and hypotonic, but there are some contractions because of the intrinsic response of the smooth muscle to stretch.

(Ref. Ganong 22th Edition; page 728)

Effects of denervation : When the afferent and efferent nerves are both destroyed, as they may be by tumors of the cauda equina or filum terminale, the bladder is flaccid and distended for a while. Gradually, however, the muscle of the *decentralized bladder* becomes active, with many contraction waves that expel dribbles of urine out of the urethra. The bladder becomes shrunken and the bladder wall hypertrophied. The reason for the difference between the small, hypertrophic bladder seen in this condition and the distended, hypotonic bladder seen when only the afferent nerves are interrupted is not known. The hyperactive state in the former condition suggests the development of denervation hhpersensitization even though the neurons interrupted are preganglionic rather than postganglionic.

(Ref. Ganong 22th Edition; page 728)

Effects of spinal cord transection : During spinal shock, the bladder is flaccid and unresponsive. It becomes overfilled, and urine dribbles through the sphincters (*overflow incontinence*). After spinal shock has passed, the voiding reflex returns, although there is, of course, no voluntary control and no inhibition or facilitation from higher centers when the spinal cord is transected. Some paraplegic patients train themselves to initiate voiding by pinching or stroking their thighs, provoking a mild mass reflex. In some instances, the voiding reflex becomes hyperactive. Bladder capacity is reduced, and the wall becomes hypertrophied. This type of bladder is some times called the *spastic neurogenic bladder*. The reflex hyperactivity is made worse by, and may be caused by, infection in the bladder wall.

(Ref. Ganong 22th Edition; page 728)

Kidney function tests

A. *Routine examination of urine* :
   i. Physical examination
      a. Quantity
      b. Colour
      c. Appearance
      d. Presence of sediment
      e. Specific gravity
      f. Osmolarity
   ii. *Chemical examination* :
      a. pH
      b. Protein (mainly albumin)
      c. Glucose
      d. Ketone bodies
      e. Bilirubin
      f. Urobilinogen
      g. Bile salts
      h. Blood
      i. Chyle
         True chyle (fat particles)
         Pseudochyle (a lecithin component of globulin)
      j. Porphyrins
   iii. *Microscopic examination* :
      a. Organized deposits
         1. Cells
            * Epithe.lial cell
            * RBC
            * Pus cell
         2. Casts
            * Cellular
            * Granular
            * Hyaline
            * Pigmented
         3. Bacteria
         4. Mucous, animal parasites, spermatozoa.
      b. Unorganized deposits :
         1. Crystals & amorphous chemicals.

B. Blood analysis :
   i. Blood urea level
   ii. BUN (blood urea nitrogen)
   iii. Plasma uric acid
   iv. Plasma creatinine
   v. Plasma electrolytes.

C. Clearance tests :
   i. Creatinine clearance test (usually used)
   ii. Inulin clearance test

D. Special tests :
   i. Water loading test
   ii. Water deprivation test 5 Acidification test

E. Immaging tests :
   i. Plain X- ray of KUB region

ii. Intravenous urography (IVU)
iii. Ultrasonogram
iv. CT scan
v. Pyelograph
vi. Renal biopsy.

Protein test : Protein coming from glomerulus or urinary tract can be identified by examination of urine.

i. If protein is more than 300mg/day : Proteinuria
ii. If protein is 30 mg/day : Bleeding from lower urinary tract.
iii. If protein is between 300 : 30 mg/day it is called microprotein.
iv. More than 200 mg/day : Abnormal
v. Less than 200 mg/day : Normal.

Creatinine clearance test : It is usually used to measure glomerular filtration rate because it is easy to determine and approximates inulin clearance.

Normal :

i. Male : 90-1 10 mI/mm
ii. Female : 80-125 mI/mm

Q.00. **Do you think determination of specific gravity of urine is a kidney function test? If so why?**

Ans. Yes, determination of specific gravity of urine is one of the kidney function test. Because depending on the types of substances cleared by kidneys, specific gravity of urine vary tremendiously from 1.045 to 1.002.

Specific gravity of urine indicates the concentrating power of kidney. So fall of specific gravity indicates fall of concentrating power of kidney. That is kidney excrets more dilute urine.

Diuresis

i. *Definition* : Diuresis means excretion of large vloume of dilute urine i.e hypotonic urine.

ii. *Types* : It is of 2 types :
   a. Water diuresis
   b. Osmotic diuresis.

Difference between the water and osmolar diuresis

Water diuresis	*Osmotic diuresis*
1. It is the increased loss of excessive water in urine due to increase water intake or lack of ADH.	1. It is the increased loss of water in urine due to the presence of the osmotically active substance which prevent tubular reabsorption of water.
2. Reabsorption of water is normal in PCT.	2. Reabsorption of water decreases from PCT.
3. Water is not reabsorbed from DCT and collecting tubule due to lack of ADH.	3. Water is not reabsorped from DCT and collecting tubule due to presence of osmotically active particle.
4. Electrolytes are not lost.	4. Significant amount of electrolytes lost in the urine.
5. Counter-current mechanism does not affected.	5. Counter current mechanism is affected.

Mechanism of action of various diuretics.

Agent	*Mechanism of action*
Water	Inhibits vasopressin secretion.
Ethanol	Inhibits vasopressin secretion.
Antagonists of V_2 vasopressin on receptors	Inhibit action of vasopressin collecting duct.
Large quantities of osmotically active substances such as mannitol and glucose	Produce osmotic diuresis.
Xanthines such as caffeine and theophylline	Decrease tubular absorption of Na^+ and increase GFR.
Acidifying salts such as $CaCl_2$ NH_4CI	Supply acid load; H^+ is and buffered, an anion is excreted with Na^+ when the ability other kidneys to replace Na^+ with H^+ is exceeded.
Carbonic anhydrase inhibitors such as acetazolamide (Diamox)	Decrease H^+ secretion, with resultant increase in Na^+ and K^+ excretion.
Metolazone (Zaroxolyn), thiazides such as chlorothiazide (Diuril)	Inhibit Na^+ and K^+ reabsorption in the early portion of the distal tubule.
Loop diuretics such as furosemide (Lasix), ethacrynic acid (Edecrin), and bumetanide	Inhibit Na^+-K^+-$2CI^-$ cotransport in the medullary thick ascending limb of the loop of Henle.
K^+- retainining natriuretics such as spironolactone (Aldactone), triamterene (Dyrenium), and amiloride (Colectril).	Inhibit Na^+-K^+ "exchange" in the distal portion of the distal tubule & the collection duct by inhibiting the action of aldosterone (spirono lactone) or by inhibiting Na^+ reabsorption (triamterene, amiloride).

(Ref.Ganong 22th Edition; Page-725)

Dialysis

Definition : Dialysis is the treatment of renal failure by dialysis with an artificial kidney.

i. *Introduction* : Dialysis causes removal of toxic waste products and restoration of body fluid volume and composition toward normal. Dialysis cannot maintain completely normal body fluid composition and cannot replace all the multiple functions performed by the kidney. Thousands of people with irreversible renal failure or even total kidney removal are being maintained for 15 to 20 years by dialysis with artificial kidneys.

ii. *Indication* : Acute or chronic severe loss of kidney function

iii. *Basic principles of dialysis* : The basic principle of the artificial kidney is to pass blood through minute blood channels bounded by a thin membrane. On the other side of the membrane a *dialyzing fluid* into which unwanted substances in the blood pass by diffusion.

In addition to diffusion of solutes, mass transfer of solutes and water can be produced by applying a hydrostatic pressure to force the fluid and solutes by the process of filtration across the membranes of the dialyzer, such filtration is called *bulk flow*.

To prevent coagulation of blood in the artificial kidney, a small amount of heparin is infused into the blood as it enters the artificial kidney.

iv. The *rate of movement of solute* across the dialyzing membrane depends on :

a. The concentration gradient of the solute between the two solutions
b. The permeability of the membrane to the solute.
c. The surface area of the membrane
d. The length of time that the blood and fluid remain in contact with the membrane.

(Ref. Guyton & Hall 11th Edition; page 414)

Q. 01. **What is the relationship of hypertension and kidneys disease?**

Ans. Renal diseases i.e glomerulonephritis, pyelonephritis, polycystic kidney disease may lead to *secondary hypertension.*

Specific tubular disorders

i. ***Renal Glycosuria***- *Failure of the kidneys to reabsorb glucose* : The blood glucose concentration may be normal, but the transport mechanism for tubular reabsorption of glucose is greatly limited or absent. Consequently, despite a normal blood glucose level, large amounts of glucose pass into the urine each day. Because diabetes mellitus is also associate with the presence of glucose in the urine, renal glycosuria, which is a relatively benign condition, must be ruled out before making a diagnosis of diabetes mellitus.

(Ref. Guyton & Hall 11th Edition; page 413)

ii. ***Aminoaciduria***- *Failure of the kidneys to reabsorb amino acids)* : Some amino acids share mutual transport systems for reabsorption, whereas other amino acids have their own distinct transport systems.

Rarely, a condition called *generalized aminoaciduria* results from deficient reabsorption of all amino acids; more frequently, deficiencies of specific carrier systems may result in-

a. Essential cystinura, in which large amounts of cystine fail to be reabsorbed and often crystallize in the urine to form renal stones.
b. *Simple glycinuria*, in which glycine fails to be reabsorbed
c. Beta-aminoisobutyric-aciduria, which occurs in about 5 percent of all people but apparently has no major clinical significance.

(Ref. Guyton & Hall 11th Edition; page 413)

iii. ***Renal hypophosphatemia***- *Failure of the kidneys to reabsorb phosphate* : The renal tubules fail to reabsorb large enough quantities of phosphate ions when the phosphate concentration of the body fluids falls very low.

a. *Effects* : This condition usually does not cause serious immediate abnormalities because phosphate concentration of the extracellular fluids can vary widely without causing major cellular dysfunction. Over a long period, a low phosphate level causes diminished calcification of the bones, thus causing the person to develop rickets.

This type of rickets is refractory to vitamin D therapy in contrast to rapid response of the usual type of rickets.

(Ref. Guyton & Hall 11th Edition; page 413)

iv. ***Renal tubular acidosis***- *Failure of the tubules to secrete hydrogen ions* : The renal tubules are unable to secrete adequate amounts of hydrogen ions.

a. *Effects* : Large amounts of sodium bicarbonate are continually lost in the urine. This causes a continued state of *metabolic acidosis.*
b. Cause : Hereditary disorders or it can occur as a result of widespread injury to the renal tubules.

(Ref. Guyton & Hall 11th Edition; page 413)

v. ***Nephrogenic diabetes insipidus***- *Failure of the kidneys to respond to antidiuretic hormone* : Occasionally, the renal tubules do not respond to antidiuretic hormone, causing large quantities of dilute urine to be excreted. As long as the person is supplied with plenty of water, this condition seldom causes severe difficulty. However, when adequate quantities of water are not available, the person rapidly becomes dehydrated.

(Ref. Guyton & Hall 11th Edition; page 414)

vi. ***Fanconi's Syndrome-*** *A generalized reabsorptive defect of the renal tubules* :

Causes : There are multiple causes of Fanconi's syndrome, which results from a generalized inability of the renal tubular cells to transport various substances. Some of these causes include-

a. Hereditary defects in cell transport mechanisms.
b. Toxins or drugs that injure the renal tubular epithelial cells.
c. Injury to the renal tubular cells as a result of ischemia.

Effects : The proximal tubular cells are especially affected in Fanconi's syndrome caused by tubular injury because these cells reabsorb and secrete many of the drugs and toxins that can cause damage.

Manifestation : Fanconi's syndrome is usually associated with increased urinary excretion of virtually all amino acids, glucose, and phosphate.

In *severe cases*, other manifestations are also observed, such as-

a. Failure to reabsorb sodium bicarbonate, which results in *metabolic acidosis*.
b. Increased excretion of potassium and sometimes calcium.
c. Nephrogenic diabetes insipidus.

(Ref. Guyton & Hall 11th Edition; page 414)

Thirst

The conscious desire for water intake is called thirst.

Thirst stimuli :

i. Intracellular dehydration.
ii. Stimulation of thirst by angiotensin.
iii. Haemorrhage and low cardiac output.
iv. Dryness of the mouth.

(Ref. Guyton & Hall 11th Edition)

Dehydration

Dehydration is a condition resulting from excessive loss of body fluid.

Causes of dehydration :

i. Excessive loss of water from body such as sweating, cholera, diarrhoea, haemorrhage etc.
ii. Reduction of total quantity of clectrolytes
iii. Injection of hypertonic solution.

Sign of dehydration :

1. Sunken of eye ball
2. Dryness of tongue
3. Wrinkles of skin
4. Dryness and rough of skin
5. Prominence of supra orbital margin, zygomatic arch etc.

Urinary System

Introduction 13.39
Renal Circulation 13.40
GFR 13.42
Absorption & Secretion 13.43
Formation of urine 13.45
Concentration of urine 13.46
Micturation 13.47
Applied 13.47

Directions : Write 'T' for true & 'F' for false against each of the filling statement.

Introduction

Q. 01. **Primary functions of the kidney are**
- T a. tubular reabsorption
- T b. tubular secretion
- T c. glomerular filtration
- F d. glomerular reabsorption
- F e. tubular absorption.

Q. 02. **Functions of the Kidney are**
- T a. regulate blood volume and composition
- T b. help to regulate blood pressure
- T c. release erythropoietin.
- F d. participate in the synthesis of vit C
- F e. stimulate production of WBC

Q. 03. **Endocrine functions of kidney is mediated through**
- T a. renin
- T b. erythropoietin
- T c. 1, 25-dihydroxycholecalciferol
- F d. epinephrine
- F e. aldosterone.

Q. 04. **Each kidney contains about .... nephrons**
- T a. One million
- F b. Two million
- F c. Four million
- F d. 1/2 million
- F e. Three million

Q. 05. **True about nephron is**
- T a. 60 to 70% of GFR is absorbed in proximal tubule
- F b. Na is absorbed actively in descending loop of Henle
- F c. Absorption of water occurs in ascending loop of Henle
- F d. The filtrate reaching distal convoluted tubule is hypertonic with respect to surroundings.
- F e. All.

Q. 06. **Nephrons are**
- T a. are the functional units of the kindey
- T b. are constant from birth
- T c. have three basic functions.
- F d. are not microscopic structure
- F e. when injured, get regenerated

Q. 07. **Regarding nephron**
- T a. it is the functional unit of kidney
- T b. its loss is not life threatening.
- T c. consist of glomerulus.
- F d. total number in each kidney is about one trillion
- F e. it can regenerate.

Q. 08. **The length of distal convulated tubule is**
- T a. 5 mm
- F b. 2 mm
- F c. 8 mm
- F d. 12 mm
- T e. 3 mm

Q. 09. **Juxtamedullary nephrons in kidney are what percentage of total nephrons**
- T a. 15
- F b. 50
- F c. 70
- F d. 90
- F e. 30

Q. 10. **Waste products removed by kidneys are**
- T a. urea - metabolic products of amino acids.
- T b. bilirubin end products of hemoglobin
- T c. food additives.
- F d. creatinine from nucleic acid
- F e. uric acid from muscle

Q. 11. **Kidneys regulate acid-base balance by**
- T a. eliminating sulfuric acid
- T b. eliminating phosphoric acid
- T c. body fluid buffers.
- F d. generating acids
- F e. without help of lungs

Q. 12. **The osmolarity of the fluid in the**
- T a. collecting duct rises when vasopressin is secreted.
- T b. medullary interstitium can exceed 1 osmol/litre.

F c. tip of the loop of Henle is less than that of plasma.
F d. Bowman's capsules is less than that in the distal tubules.
F e. proximal convoluted tubule rises along its length.

Q. 13. **Which of the following hormones are acting on the proximal tubule?**
T a. bradykinin.
T b. prostaglandin
F c. aldosteron
F d. angiotensin II
F e. ADH

Q. 14. **The Kidney secretes**
T a. renin.
T b. erythropoietin
T c. 1,25- dihydroxycholecalciferol
F d. gastrin
F e. vasopressin.

Q. 15. **Erythropoietin is secreted by**
T a. kidney
F b. liver
F c. bone malTow
F d. adrenal cortex
F e. capillary endotheliurn.

Q. 16. **Erythropoietin level is raised by**
T a. Decreased PO_2
F b. Decreased PCO_2
F c. Decreased Hb
F d. Decreased pH
F e. None.

Q. 17. **Erythropoietin is secreted by**
T a. Kidney
F b. Lrver
F c. Adrenal cortex
F d. Bone marrow
F e. None.

Q. 18. **Site of ADH action is**
T a. Collecting tubule
F b. Proximal tubule
F c. Loop of Henle
F d. Vasa recta
F e. None.

Q. 19. **Site of ADH action is**
T a. thick ascending limb of loop of Henle
T b. collecting tubule.
F c. proximal tubule
F d. vasa recta
F e. loop of Henle

Q. 20. **Administration of ADH**
T a. increases active reabsortion of by distal tubule.
T b. decreases water loss by kidney
F c. decreases water loss by lung
F d. increases perspiration
F e. decreases active reabsorbtion of Na^+ by proximal tubule.

Q. 21. **Renin secretion is stimulated by all except**
T a. High Na^+ in proximal tubule
F b. Cardiac failure
F c. Low Na^+ in proximal tubule
F d. Sympathetic stimulation
F e. None.

Q. 22. **Renin secretion is stimualted by**
T a. hypoxia.
T b. cardiac failure
T c. low Na^+ in the proximal tubule
T d. sympathetic stimulation
F e. high Na^+ in proximal tubule

Q. 23. **The renin angiotensin aldosterone system regulates**
T a. K^+ balance
T b. Na^+ balance
T c. fluid volume
T d. blood pressure
F e. nitrogen balance.

Q. 24. **Agents causing contraction of mesangial cells are**
T a. angiotensin-II.
T b. endothelins
T c. vasopressin
F d. ANP
F e. dopamine

Q. 25. **Relaxation of mesangial cells of kidney is brought about by**
T a. cAMP
F b. Endothelin
F c. PGF2 vasopressin
F d. ANP
F e. dopamine

Renal Circulation

Q. 26. **In resting state the renal blood flow per minute is**
T a. 1200 - 1300 ml
F b. 200 - 500 ml
F c. 400 - 500 ml
F d. 500 - 600 ml
F e. 600 - 100 ml.

Q. 27. **The renal blood flow (in ml/minute) is :**
T a. 1260
F b. 250

F c. 800
F d. 1500
F e. 1060

Q. 28. **In humans, effective renal blood flow is :**
T a. 625
F b. 425
F c. 525
F d. 725
F c. 225

Q. 29. **Renal blood flow falls**
T a. during emotional stress
T b. after moderate hemorrhage
F c. about 10% when arterial pressure falls 10% below normal.
F d. about 5% when metabolic activity in the kindney falls by 5% below normal
F e. gradually from the inner medulla to outer cortex per unit weight of tissue.

Q. 30. **Renal blood flow is increased when**
T a. glucocorticoids increases
T b. high protein diet intake increased
T c. hyperglycemia occurs
F d. hypoglycemia occurs
F e. aging occurs.

Q. 31. **Renal plasma flow is 600 ml/minute andthe hematocrit is 40%. What is the renal blood flow in ml/minute?**
T a. 1000
F b. 1500
F c. 900
F d. 1800
F e. 950.

Q. 32. **Effective renal plasma flow is**
T a. 630 ml/minute.
T b. measured by C_{PAH}
F c. measured by Tm of PAH
F d. 125 ml/minute.
F e. measured by C_{IN}

Q. 33. **Hydrostatic pressure in renal glomerular capillaries**
T a. is higher than in most other capillaries at heart level..
T b. falls as the oncotic pressure rises along the length of the capillary.
F c. is lower than pressure in efferent arteriole
F d. rises when afferent arterioles constrict.
F e. falls by 10% when arterial pressure falls by 10%

Q. 34. **Approximate pressure in renal circulation**
T a. renal artery : 100 mm of Hg.
T b. afferent arteriole : 85 mm of Hg.
T c. renal vein : 4 mm of Hg.
F d. glomerular capillaries : 10 mm of Hg.
F e. efferent arteriole : 60 mm of Hg

Q. 35. **Glomerular capillary hydrostatic pressure**
T a. reduces by afferent arteriolar resistance.
T b. is higher than that in efferent arteriole
T c. regulates GFR
F d. is normally 32 mm of Hg
F e. is increased if GFR is decreased

Q. 36. **Filterability of substance by glomerular capillaries**
T a. albumin : 0.005
T b. water : 1.0
F c. sodium : 0.8
F d. glucose : 0.75
F e. inulin : 0 .75

Q. 37. **Autoregulation of renal blood flow**
T a. is seen when the kidney is prefused at pressures between 90-220 mm of Hg
T b. is present in denervated kidney
T c. is partly due to direct contractile response of the efferent arteriole to stretch.
F d. does not occur in the kidney
F e. can be prevented by the administration of drugs that excites the vascular smooth muscles.

Q. 38. **Autoregulation is seen in**
T a. Muscles
T b. Kidneys
T c. Brain
F d. Liver
F e. All.

Q. 39. **Kidneys regulate arterial pressure by**
T a. excreting water and sodium
T b. secreting renin
T c. renin angiotensin mechanism
F d. excreting vasoactive factors
F e. G cells in the efferent arterioles.

Q. 40. **When a patient's mean arterial blood pressure falls by 50%**
T a. there is an increase in the circulating aldosterone level.
T b. renal vesoconstriction occurs.
T c. urinary output may cease.
F d. renal blood flow falls by less than 10%
F e. glomerular filtration falls by about 50%

Q. 41. **Factors favouring filtration across the glomerular capillaries are**
T a. increase in the size of the glomerular capiliary bed.
T b. low colloidal osmotic pressure within the glomerular capillaries
T c. efferent arteriolar constriction.

F d. high colloidal osmotic pressure within the glomerular capillaries.
F e. low hydrostatic pressure within the glomerular capillaries.

GFR

Q. 42. **What is the glomerular filtration rate?**
T a. 125 ml/min
F b. 100 ml/min
F c. 150 ml/min
F d. 175 ml/min
F e. 200 ml/min

Q. 43. **Filtration barrier in the glomerular capilaries is produced by**
T a. basal lamina
F b. slit pore
F c. podocytes
F d. juxtaglomerular cells
F e. endothelial cells.

Q. 44. **One of the following does not form filtration barrier in nephrons**
T a. Mesangium
F b. Podocytes
F c. Endothelial cell
F d. Basement membrane
F e. None.

Q. 45. **Two substances that can probably be usedto determine filtration fraction are**
T a. Inulin and PAH
F b. Insulin and mannitol
F c. Urea and diodrast
F d. PAH and phenol red
F e. None.

Q. 46. **GFR is**
T a. relatively constant.
T b. increased by prostaglandin.
F c. dereased by bradykinin.
F d. increased by nitric oxide.
F e. increased by angiotesin II.

Q. 47. **The normal glomerular filtration rate is apporximately**
T a. 125 m1/minute
T b. 7.5 L/hour
T c. 180 L/day
F d. 100 ml/minute
F e. 180 L/minute

Q. 48. **Glomerular filtration rate**
T a. tends to increase in hypoproteinemia
T b. can be measured by inulin clearance test.
F c. is 60 ml/min
F d. increases during strenuous exercises
F e. tends to decrease when the efferent arteriole is constricted.

Q. 49. **Following substances are filtered by kidney**
T a. glucose :180 gm day
F b. bicarbonate : 4310 mEq/day
F c. sodium : 16420 mEq/day
F d. chloride : 19440 mEq/L
F e. urea : 12120 gm/day.

Q. 50. **Normal kidney does not allow passage of**
T a. β-globulin
F b. Lysozyme
F c. IgG
F d. Albumin
F e. None.

Q. 51. **Factors that can increase GFR**
T a. decreased plasma proteins
T b. decreased arterial pressure
F c. increase glomerular coefficient.
F d. urinary tract obstruction.
F e. increased afferent arteriolar resistance.

Q. 52. **GFR is increased when**
T a. renal blood flow is increased.
T b. glomerular capillary hydrostatic pressure increased.
F c. plasma oncotic prssure is increased.
F d. glomerular hydrostatic pressure is increaed.
F e. tubular hydrostatic pressure is increased.

Q. 53. **GFR is increased when**
T a. renal blood flow is increased
F b. plasma oncotic pressure is increased
F c. glomerular hydostatic pressure is increased
F d. tubular hydrostatic pressure is increased
F e. when blood pressure is decreased.

Q. 54. **GFR is decreased when**
T a. glomerular capillary filtration coefficient (Kf) is decreased.
T b. bowman's capsule pressure increased.
T c. glomerular capillary colloid osmotic pressure is increased.
F d. renal blood flow is increased.
F e. glomerular capillary hydrostatic pressure is increased.

Q. 55. **Renal GFR can be estimated by**
T a. Tc^{99} DTPA
F b. Tc^{99} DMCA
F c. Tc^{99} DMSA
F d. Tc^{99}
F e. Tc^{99} DT.

Q. 56. **GFR can be measured by**
- T a. C_{IN}
- T b. C_{Cr}
- F c. C_{PAH}
- F d. C_G
- F e. C_U

Q. 57. **Criteria to be fulfilled by a substance to be used for the measurement of GFR include**
- T a. to be freely filtered and neither reasorbed or secreted.
- T b. nontoxic
- T c. not metabolized in the body.
- F d. to be freely filtered only
- F e. to be freely filtered and secreted

Q. 58. **GFR is regulated by**
- T a. glomerular capillary pressure
- T b. glomerular capillary flood flow
- T c. plasma collidal osmotic pressure
- T d. effective filtration pressure
- T e. normal blood pressure.

Q. 59. **Which of the following is truly physiological**
- T a. Increased GFR
- F b. Albuminuria
- F c. Increased blood pressure
- F d. Mild pedal edema
- F e. None.

Q. 60. **Major portion of glomerular filtrate is absorbed in**
- T a. Proximal segment
- F b. Loop of Henle
- F c. Distal convoluted tubule
- F d. Collecting duct
- F d. Sprouting

Absorption & Secretion

Q. 61. **The major differences between the plasma and inter stitial fluid are in**
- T a. the concentration of Na^+
- T b. the protein content.
- F c. the concentration of Ca^+
- F d. the HCO_3^- concentration.
- F e. the organic acid concentration.

Q. 62. **Following cells are responsible for acid secretion in kidney**
- T a. I cells
- F b. P cells
- F c. Mesangial cells
- F d. Pericytes
- F e. None.

Q. 63. **The part of the nephron least permeable to water are**
- T a. ascending limb of loop of Henle
- T b. collecting tubule
- T c. collecting duct.
- F d. proximal tubule
- F e. descending limb of loop of Henle

Q. 64. **Substances that are freely filtered but not reabsorbed by the kidney include**
- T a. creatinine
- F b. urea
- F c. glucose
- F d. bicarbonate
- F e. chloride.

Q. 65. **Renal tubules normally reabsorb**
- T a. about 99% of the glomerular filtrate
- T b. all filtered HCO_3 in respiratory acidosis
- T c. all filtered amino acids.
- T d. all filtered plasma proteins.
- F e. more K^+ than $C1^-$

Q. 66. **Tubular reabsorption**
- T a. is highly selective
- T b. is very large relative to excretion
- F c. is only by passive mechanism
- F d. of water is active process
- F e. of water is passive process.

Q. 67. **Substances completely reabsorbed only in the proximal tubule are**
- T a. uric acid
- T b. glucose
- F c. water
- F d. Na^+ ions
- F e. PAH.

Q. 68. **The proximal convoluted tubules**
- T a. reabsorb most of the sodium ions in glomerular filtrate
- T b. reabsorb most of the chloride ions in glomelular filtrate.
- T c. reabsorb most of the potassium ions in glomerular filtrate.
- F d. contain juxtaglomerular cells which secrete renin.
- F e. contain the main target cells for antid uretic hormone.

Q. 69. **Proximal tubule**
- T a. shows highly selective reabsorption.
- T b. is one of the important parts of nephron.
- F c. receives fluid from glomerulus.
- F d. is in the medulla.
- F e. is connected with connective tubules.

Q. 70. **The cells of the distal convoluted tubule**
- T a. secrete hydrogen ions into the tubular lumen
- T b. form NH_4^+
- T c. reabsorb sodium in exchange for hydrogen or potassium ions
- F d. reabsorbs about 50% of water filtered by the golmeruli
- F e. determine the final composition of urine.

Q. 71. **Active reabsorption from proximal tubule are**
- T a. bicarbonate
- T b. water.
- T c. sodium
- F d. carbonic acid
- F e. hydrogen

Q. 72. **Reabsorption in the first half of proximal tubules are**
- T a. sodium
- T b. glucose
- T c. amino acid
- F d. chloride
- F e. bicarbonate.

Q. 73. **Secretion from proximal tubule are**
- T a. bile salt
- T b. oxalate
- T c. urate
- F d. amino acid
- F e. sodium.

Q. 74. **In proximal convoluted tubule**
- T a. glucose is completely reabsorbed under normal conditions
- T b. K^+ is reabsorbed.
- F c. about 90% of filtered water is reabsorbed.
- F d. renin is produced
- F e. PAH is actively reabsorbed.

Q. 75. **The loop of Henle**
- T a. actively transports Na^+ in the thick ascending limb.
- T b. is responsible for high medullary osmolarity
- T c. returns fluid of low osmolarity to the distal convoluted tubule
- F d. has a high permeability to water in the thick ascending limb of the loop of Henle.
- F e. actively pumps ions across the epithelium of the descending limb

Q. 76. **Filtration fraction**
- T a. is normally 0.16 - 0.20
- T b. is the ratio of GFR to RPF
- T c. rises when there is a fall in systemic blood pressure because of the efferent arteriolar constriction and less reduction in GFR compared to RPF
- F d. is the ratio of RPF to GFR
- F e. normally 0.60 - 0.80.

Q. 77. **Thin segment of loop of Henle is highly permeable to**
- T a. water
- T b. glucose
- T c. amino acid.
- F d. sodium
- F b. urea.

Q. 78. **The hyperosmolarity of the renal medulla is due to increased concentration of**
- T a. Na^+
- T b. urea
- F c. K^+
- F d. glucose
- F e. Cl^-.

Q. 79. **The reabsortion of water in distal convoluted tubule is under control of**
- T a. ADH
- F b. aldosterone
- F c. ACTH
- F d. cotisol
- F e. insulin.

Q. 80. **Active reabsorption of glucose occurs in the**
- T a. proximal tubule
- F b. loop of Henle
- F c. distal tubule
- F d. collecting duct
- F e. thick ascending limb of loop of Henle.

Q. 81. **Where in the kidney tubule does active reabsorbtion of Na^+ occur**
- T a. collecting duct
- T b. distal tubule
- T c. ascending limb of loop of Henle
- T d. proximal tubule
- F e. thin segment of loop of Henle.

Q. 82. **Where in the kidney, does active reabsorption of sodium ions occur?**
- T a. Collecting duct
- T b. Distal tubule
- T c. Ascending limb of Henle
- T d. All of the above
- F e. Only b and c

Q. 83. **K^+ reabsorption of the kidney tubules occurs**
- T a. being coupled with Na^+ loss
- T b. only in proximal tubule
- T c. under the influence of aldosterone.
- F d. partly in the proximal and distal tubule
- F e. under the influce of ADH

Q. 84. **Potassium reabsorption in kidneys occur**
- T a. Coupled with sodium ions
- F b. Partly in POT and OCT
- F c. Under the influence of ADH
- F d. Only in POT
- F e. All.

Q. 85. **Ammonia in the Kidney tubules is excreted in exchange for**
- T a. HCO_3
- F b. Na^+
- F c. Cl^-
- F d. PO_4^{--}
- F e. All.

Q. 86. **Extracellular fluid volume is maintained by**
- T a. ADH.
- T b. aldoesterone.
- T c. osmolarity of plasma.
- T d. plasma K^+ level.
- F e. oxytocin.

Formation of urine

Q. 87. **Urine formation results from**
- T a. reabsorption from renal tubules.
- T b. glomenular filtration.
- T c. secretion from peritubular capillaries.
- F d. ultrafiltration of afferent arteriole.
- F e. dialysis of collecting tubules.

Q. 88. **In normal healthy subjects, urinary**
- T a. pH falls as dietary protein is increased
- F b. specific gravity ranges from 1.002 to 1.010
- F c. osmolarity ranges from 200 to 400 mOsmo/L
- F d. volume is SLIday
- F e. calcium excretion is increased by parathormone.

Q. 89. **Abnormal urinary constituents are**
- T a. acetone.
- T b. albumin
- T c. amino acid
- F d. creatinine
- F e. urea

Q. 90. **Abnormal urinary constituents include**
- T a. ketone bodies
- T b. glucose.
- T c. albumin
- T d. amino acid
- F e. creatinine

Q. 91. **Urea**
- T a. may cause diumsis when its blood conctration is increased.
- T b. has similar molar concentration in plasma as glucose.
- T c. concentration rises in tubular fluid as the glomerular filtrate passes down the nephron.
- F d. is actively secreted by the renal tubular cells into the tubular fluid.
- F e. concentration in blood may rise ten fold after a high protein meal.

Q. 92. **True about creatine**
- T a. Measures GFR
- F b. It is a muscle protein
- F c. High energy compound
- F d. None
- F e. All.

Q. 93. **Normal levels of creatinine in serum is**
- T a. 0.6 to 1.2 mg%
- F b. 1 to 2 mg%
- F c. 0.01 to 0.04 mg%
- F d. 0.04 to 0.1 mg%
- F e. 0.14 to 0.2 mg%

Q. 94. **The normal non-fasting blood ketone level is**
- T a. 2-10 mg%
- F b. 0.1-0.5 mg%
- F c. 0.5-2 mg%
- F d. 100-500 mg%
- T c. 20-25 mg%

Q. 95. **U/P ratio of creatinine (mg/dl) is**
- T a. 150
- F b. 0
- F c. 0.6
- F d. 60
- F e. 300.

Q. 96. **The renal clearance of**
- T a. pAH continues to rise as the plasma concentration of pAH rises.
- F b. Creatinine indicates glomerular filtration rate
- F c. Insulin is lower than that of urea
- F d. Chloride increases after an injection of aldosterone
- F e. All.

Q. 97. **When the clearance ratio of a substance is 1, the substance may be**
- T a. inulin
- F b. glucose
- F c. amino acids
- F d. sodium
- F e. PAH.

Q. 98. **What is the urea clearance?**
- T a. 44 ml/min
- F b. 4.4 ml/min

F c. 88 ml/min
F d. 440 ml/min
F e. 22 ml/min

Q. 99. **Inulin clearance closely resembles**
T a. GFR
F b. Renal plasma flow
F c. Creatinine clearance
F d. PAH clearance
F e. None.

Q. 100. **Inulin clearance is equal to**
T a. 125 ml/min
F b. 55 ml/min
F c. 625 ml/min
F d. 40 ml/min
F c. 105 ml/min

Q. 101. **True statement regarding creatinine clearance is**
T a. Represents GFR
F b. 80 ml/mm
F c. Most accurate renal function test
F d. Represents tubular function
F e. None.

Q. 102. **Transport maximum (Tm) means**
T a. Maximum reabsorption & secretion
F b. Maximum amount of glomerular filtration /min
F c. Substance cleared from plasma /min
F d. Amount of toxic substances excreted /min.
F e. None.

Q. 103. **The maximum amount of each substance that can be trasported in each minute by kidney tubules is called**
T a. tubular maximum
F b. transport maximum
F c. secretion maximum
F d. tubular load
F e. filtered load.

Q. 104. **Transport Maximum of**
T a. phosphate : 0.10 mM/min
T b. lactate : 75 mg/min.
F c. glucose : 180 mg/min
F d. amino acids : 15 rmM/min
F e. plasma protein : 90 mg/min

Q. 105. **Regarding transport maximum (Tm) of glucose**
T a. when the TmG is exceeded glucose appears in the urine
T b. it is about 375 mg/min
F c. it is about 650 ml/min
F d. it is high in diabetes mellitus
F e. it is low in diabetes insipidus.

Q. 106. **Which of the following has no Tm value?**
T a. Urea
F b. Albumin, arginine
F c. Betahydroxybutyrate, glucose
F d. Glucose, haemoglobin, phosphate,
F e. Sulfate, uric acid

Q. 107. **Substances that have no transport maxmum include**
T a. chloride
T b. Urea.
F c. amino acid
F d. plasma protein
F e. creatinjne

Q. 108. **Tubular maximum for kidney in practice and is actually less than the calculated value because**
T a. it depends on renal threshold
T b. different nephron have different reabsorp tion capacities
F c. it depends on GFR
F d. it depends on renal blood flow
F e. its depends on decrease blood pressure.
T c. reabsorbtion is complete below a certain threshold value.

Q. 109. **Tm (Transport maximum) limited reabsorption of a substance implies that**
T a. excretion rate is zero until Tm value is reached.
T b. reabsorbtion is active
F c. reabsortion is critically related to tubular transit time
F d. renal clearance falls with its plasma concentration
F e. All.

Q. 110. **Tubular maximum for kidney in practice is actually less than the calculated value because**
T a. Different nephrons have different lengths
F b. Depends on GFR
F c. Depends of Renal blood flow
F d. Depends on blood pressure
F e. All.

Concentration of urine

Q. 111. **Hyperosmolarity of the renal medullary interstium during countercurrent mechnism is due to**
T a. active transport of Na^+ from thick segment.
T b. co-transport of K^+ & $C1^-$ from thick segment.
T c. active transport of ions from the collecting duct.
T d. passive diffusion of urea from inner medullary collecting duct
F e. active transport of K^+ from colleting duct.

Q. 112. **The hyperosmolarity of the renal medulla is due to increased content of**
- T b. Na
- F a. K
- F c. Glucose
- F d. Na^+
- F e. Cl

Q. 113. **The ability of the kidney to concentrate urine is due to**
- T a. presence of juxtamedullary nephrons
- T b. presence of countercurrent multiplier (long loop of Henle)
- T c. presence of countercurrent exchanger (vasa recta)
- T d. presence of ADH
- F e. presence of aldosterone.

Q. 114. **Which one of the following is not responsible for concentration of urine in the kidneys?**
- T a. Aldosterone
- T b. Angiotensin II
- T c. Vasopressin
- F d. Epinephrine
- F d. Norepinephrine

Q. 115. **Which one of the following is not responsible for concentration of urine in the kidneys?**
- T a. Epinephrine.
- F b. Aldosterone
- F c. Angiotensin II
- F d. Vasopressin
- F e. All.

Q. 116. **The excretion of sodium (meq) in 24 hours is**
- T a. 150
- F b. Zero
- F c. 50
- F d. 250
- F e. 75

Q. 117. **In addition to kidney, counter current multiplier system is present in**
- T a. Crypts of gastric submucosa
- F b. Bone
- F c. Muscles
- F d. Skin
- F e. All.

Micturation

Q. 118. **The urge for micturition is felt when the bladder is filled with**
- T a. 300 - 400cc of urine
- F b. 700 - 800cc of urine
- F c. 100 - 200cc of urine
- F d. 500 - 700cc of urine
- F e. 70 - 80cc of urine

Q. 119. **True statement among the following is**
- T a. Bladder emptying cannot occur if volume < 100 ml
- F b. Bladder muscle contains intrafusal fibres
- F c. Pressure increases in bladder vary linearly with time
- F d. One litre of fluid intake results in complete excretion in 1 hour
- F e. All.

Q. 120. **In a normal adult the desire for micturition is felt**
- T a. When about 300-400 cc of urine has collected in the bladder
- F b. When about 100-200 cc of urine has collected in the bladder
- F c. When about 600-800 cc of urine has collected in the bladder
- F d. When about 1000 cc of urine has collected in the bladder
- F e. When about 100-150 cc of urine has collected in the bladder.

Applied

Q. 121. **Factors that increase renal calcium excretion are**
- T a. decreased PTH
- T b. increased PTH
- F c. increased plasma phosphate
- F d. metabolic acidosis
- F e. decreased blood pressure.

Q. 122. **A long standing increase in arterial PCO_2 (respiratory acidosis) leads to an increase in**
- T a. renal bicarbonate formation
- T b. urinary ammonium salts
- T c. plasma potassium concentration
- F d. the ratio of monohydrogen to dihydrogen phosphate in urine
- F e. urinary bicarbonate excretion.

Q. 123. **When pH of the blood is too low, the ions that secrete into the nephon from the surounding capillaries are**
- T a. H^+
- T b. NH^{4+}
- F c. Na^+
- F d. HCO_3^-
- F e. Cl^-.

Q. 124. **Alkalosis accurs whenever pH is above:**
- T a. 7.40
- T b. 7.04
- F c. 7.000

F d. 7.24
F e. 7.36

Q. 125. **Respiratory acidosis can cause**
T a. Increased PCO_2 and decreased P^H
F b. Decreased PCO_2 and decreased P^H
F c. Increased PCO_2 and increased P^H
F d. Decreased PCO_2 and increased P^H
F e. All.

Q. 126. **Metabolic alkalosis associated with prolonged vomiting is due to primarily to loss of**
T a. Chloride
F b. Sodium
F c. Potassium
F d. Hydrogen ion
F e. All.

Q. 127. **At high altitude one will develop**
T a. tetany.
T b. respiratory alkalosis
F c. respiratory acidosis
F d. metabolic acidosis
F e. metabolic alkalosis.

Q. 128. **A patient with chronic renal failure usually has an increased**
T a. blood urea
T b. blood uric acid
T c. acid-base problem on a high protein diet.
F d. creatinine clearance
F e. acid-base disturbance when he or she vomits.

Q. 129. **Dialysis fluid used in the treatment of renal failure should not contain**
T a. urea
T b. creatinine
T c. phosphate
F d. glucose
F e. Na^+.

Q. 130. **Diuresis is caused by**
T a. Mannitol
T b. Glycerol
T c. Urea
T d. All of the above
F e. None.

Q. 131. **Which is seen in high altitude**
T a. Respiratory alkalosis
F b. Metabolic alkalosis
F c. Respiratory acidosis
F d. Metabolic acidosis
F e. None.

Q. 132. **Injection of hypertonic saline into which area causes diuresis**
T a. Supraoptic nucleus
F b. Paraventricular nucleus
F c. Preoptic nucleus
F d. Posterior pituitary
F e. None.

Q. 133. **Addis test is used for :**
T a. Urinary sediment
F b. Urinary sugar
F c. Blood lacted
F d. Serum magnesium
F e. All.

Q. 134. **Renal calculi is seen in**
T a. Hyperparathyroidism
F b. Hyperthyroidism
F c. Cushing disease
F d. Addisons disease
F e. All.

Q. 135. **In renal glycosuria, the renal threshold for glucose is**
T a. Low
F b. High
F c. Same
F d. Greatly increased
F e. All.

14
Metabolism

Metabolism

Definition : It is the sum total of anabolism and catabolism. ***or***
It may be defined as a series of specific biochemical reaction occuring within living organism, catalysed by enzymes, co-enzymes, co-factors and governed by hormones and vitamins.

It consists of anabolism and catabolism.

i. ***Anabolism*** : The synthesis processes or the energy consuming processe those convert small molecules into bigger form for binding up of storage, structural or functional material are collectively known as anabolism.

The chain of reacton of anabolism are :

i. Synthesis of glycogen from glucose- glycogenesis
ii. Lipid synthesis-lipogenesis.
iii. Protein synthesis.
iv. ketone body synthesis.
v. Urea synthesis.
vi. Cholesterol synthesis.

ii. ***Catabolism*** : The breakdown processes or the processes that convert bigger molecules into smaller form for the supply of energy are collectively known as catabolism.

The chain of reaction of catabolisms are :

i. Break down of glycogen into glucose-glycogenolysis.
ii. Break down of glucose- glycolysis.
iii. Break down of lipid-lipolysis.
iv. Protein catabolism.

Steps of catabolism : Catabolism takes place in three broad stages-

First stage : This is the preparatory stage by which the simple fragments derived from complex food stuff, pass into the metabolic platform.

Second stage: It includes the sequence of biochemical reactions, through which the end products of 1st stage are transformed into active acetate or Alpha-ketoglutarate or oxaloacetic acid. About 30% of the total energy is liberated during these reaction.

Third stage : It includes the sequence of biochemical reactions, through which, the end products of second stage are oxidized into CO_2, H_2O & energy. It liberates about 70% of total energgy.

Importance of metabolism : The proximate principles of food are oxidized, producing carbondioxide, water and energy. A part of this energy is stored and rest is utilized for-

i. Protein synthesis and growth of the body.
ii. Muscular activity.
iii. Secretion by the glands.
iv. Maintenance of membrane potential by nerve and muscle fibres.
v. Absorption of food from gastrointestinal tract.

Free energy

The amount of energy liberated by complete oxidation of a food is called free energy of food. Free energy is usually expressed in terms of calories per mole of food substances. For instance, the amount of free energy liberated by oxidation of 1 mole of glucose (180 gms glucose) is 6,86,000 calories.

(Ref. Guyton 11th edition)

Coupled energy

The amount of energy liberated by oxidation of a food with cellular oxygen which energy is not in free but coupled with systems responsible for various physiological function. Energy in the form of ATP, GTP, ADP etc.

Bond energy (energy rich compounds)

Inside the body there are some organic molecules, mostly phosphates or S-H groups which actively participate in metabolic reactions, which has the capacity to take energy during synthesis and liberate energy during their breakdown. The energy which remain in this form is called bond energy.

Though called bond energy, the energy is not located in the bond, but they remains in the structural configuration of the molecules.

Advantage of bond energy : The advantage of bond energy is such that the phosphate group can be directly transferred to another organic moleule along with transfer of energy, which results in the formation of another energy rich phosphorylated molecule.

Exergenic reaction

In the intermediary metabolism of carbohydrate, protein and fat the reaction in which energy is liberated in coupled form or which is useable for the body.

Endergenic reaction

During metabolic change the reaction in which the liberated energy is not useable, for the body is called endergenic reaction.

High energy substances

The substances which liberates large amount of energy (10-12 kcal/mol) when hydrolysed are known as high energy substance e.g ATP, ADP, creatinine phosphate, phosphopyruvic acid, acetyl phosphate, GTP etc.

High energy sbustance or phosphate compounds : The high

energy phosphate bond is designated as pH. The high energy phosphate compounds help in-

i. Transfer of phosphate group easily without loss of much energy.
ii. The energy is stored for utilization in the synthetic process.
iii. Help in oxidative phosphorylation essential for many substances in the body.
iv. When break down, a part of energy is converted into heat & help in thermal balance.

***Adenosine triphospate** (ATP)*

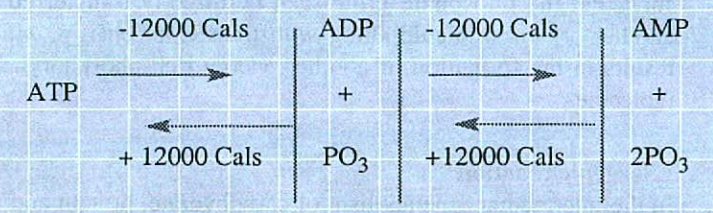
i. *Definition* : ATP (Adenosine triphosphate) is a high energy phosphate compound which is the storage form of energy in the body.

ii *Composition* :
   a. Adenine
   b. Ribose
   c. Phosphates.

iii. *Sources* :
   a. Oxidative phosphorylation
   b. Glycolysis
   c. TCA cycle.

iv. *Functions* : It helps in
   a. Synthetic process
   b. Muscular contraction
   c. Nerve conduction
   d. Active transport
   e. Secretion by the gland.

v. *Role of ATP in metabolism* : Removal of each phosphate radicle liberates 12000 cals of energy. After loss of one phosphate from ATP the compound becomes ADP and after lossing of the second phosphate radicle the compound becomes AMP.



Low energy substances

The substances which liberate relatively small amount of energy (2-3 kcal/mol) on hydrolysis are known as low energy substance e.g Glucose 1-P, Glucose 6-P, Fructose 1-6 diphosphate etc.

Active acetate

The acetyl derivatives of high energy compounds are known as active acetate. When Co-A reacts with acetic acid, acetyl Co-A is formed which is rich in energy.

Q. ***Why Acetyl Co-A is called "active acetate"?***

Ans. Acetyl CoA has a much energy content than acetic acid, So, acetyl Co-A is called active acetate i.e. formation of 1 molecle of acetyl Co-A compound equivalent to the formation of 1 molecule of ATP.

Intermediary metabolism

It is the sum total of those sepecific chemical changes that takes place for a particular type of food from its absorption upto energy yeild.

Example : Glucose → Glycogenesis → Glycogenolysis → Glycolysis → TCA cycle → CO_2, H_2O & energy.

Phosphorylation

The term phosphorylation includes all chemical reactions in the body which require combination of phosphoric acid.

Dephosphorylation : The term includes all chemical reactions in the body where phosphoric acid is dissociated from the compound.

Importance of phosphorylation : Physiological importance of phosphorylation are-

A. *In relation to carbohydrate :*
   i. Absorption of carbohydrate through intestinal mucosa and reabsorption of glucose from renal tubules are helped by phosphorylation.
   ii. Formation of glycogen from glucose & breakdown of glycogen into glucose in the liver & muscle also takes place through phosphorylation.

B. *In relation to fat :*
   i. During absorption of fats; neutral fats & phospholipids are synthesized in the absorbing epithelium by phosphorylation with the help of enzyme phosphorylase.
   ii. Liver synthesized phospholipid specially lecithin.
   iii. Kephalin or cephalin, one of the phospholipids is built up by phosphorylation which initiates blood clotting.
   iv. Each cell can synthesize its own phospholipids locally by phosphorylation.

C. *In relation to protein :*
   i. All the phosphoproteins (Nucleo-protein, caseinogen) are synthesized with the help of phosphorylation.

D. *Miscellaneous :*
   i. Phosphorylation takes an important part in tissue oxidation during which proteins, fats and carbohydrates are finally broken down.
   ii. Some member of Vitamin-B group are phosphorylated compounds, e.g thiamine pyrophosphate.
   iii. Formation of bone i.e deposition of inorganic phosphoric acid compounds occur by phosphorylation.

Control of phosphorylation :

1. Enzymes : The enzymes that take part in this process are phosphorylase, phosphatase etc.
2. Hormones :
   a. Adrenal cortex : Glucocorticoids inhibit phosphorylation.

b. Anterior pituitary : By ACTH it exerts a superior control on phosphorylation, through adrenal cortex.

3. Inorganic Salts : Na^+ may have some effect on phosphorylation.

Q. ***How glucose is phosphorylated?***

Ans. Immediately upon entry into cells, glucose is phosphorylated by ATP. Phosphorylation is performed by the enzyme, glucokinase.

$$\text{Glucose} \xrightarrow[\text{ATP}]{\textit{Glucokinase}} \text{Glucose-6-Phosphate.}$$

Phosphorylation of glucose is almost completely irreversible except in liver cells, renal tubule and intestinal epithelial cells.

Oxidative phosphorylation

Detinition : Oxidative phosphorylation is a coupled reaction where there is oxidation of the substrate as well as phosphorylation i.e. synthesis of ATP from ADP & Pi.

Indication of oxidative phosphorylation : It indicates that during biological oxidation energy is released which is captured in the form of high energy phosphate bond.

Site : Mitochondria

Types :

1. *Substrate level phosphorylation* : Here formation of high energy phosphate takes place on the substrate without undergoing into the respiratory chain.

   Example :

   i. Conversion of phosphoenol pyruvate by *phosphoenol pyruvate kinase* - the release of energy by the hydrolysis of high energy bond of phosphate is utilized for the synthesis of ATP.

   ii. Succinyl CoA → Succinate

   GDP + Pi → GTP ⇢ ATP

2. *Respiratory chain level phosphorylation* : Here formation of high energy phosphate takes place as a result of transfer of H^+ and electrons through the respiratory chain to oxygen.

   Examples :

   i. Isocitrate is converted to oxalosuccinate

   ii. Succinate is converted into fumerate etc.

Mechanism of oxidative phosphorylation :

The exact mechanism of oxidative phosphorylation has not been elucidate. However three proposed mechanism are-

1. *Chemical coupling hypothesis* : Transfer of electrons produces a covalent high energy intermediate compound, which acts as precursor of ATP.

2. *Chemiosmotic coupling hypothesis* : During oxidation H^+ (protons) are produced in the respiratory chain, which are ejected out of the inner mitochondrial membrane. Accumulation of proton on outer face of the inner mitochondrial membrane produces an electro-chemical potential difference, which forces the membrane bound ATP synthetase to generate ATP from ADP + Pi.

3. *Conformational coupling hypothesis* : In this hypothesis it is presumed that energy released during electron transfer is conserved in the conformational changes of the molecules which drive the generation of ATP.

Cyclic AMP

i. *Definition* : It is a cyclic nucleotide. Chemically it is 3', 5'-adenosine monophosphate.

ii. *Synthesis* : It is synthesized in the cell from ATP under the influence of adenyl cyclase in the presence of Mg ions.

iii. *Degradation* : It is degraded in the tissues by its conversion to 5'-AMP in a reaction catalyzed by the phosphodiesterase.

iv. *Biomedical importance* :

   a. It acts as second messenger for many polypeptide hormones.

   b. It activates or inactivates the enzymes that catalyze key reactions of metabolism.

Biological oxidation

Oxidation : Chemically oxidation is defined as the removal of electrons.

$$Fe^{++} \xrightarrow{e^-} Fe^{+++}$$

Oxidation means :

i. Combination with O_2 or

ii. Removal of H^+ or dehydrogenation

Reduction : Loss of O_2 and addition of H^+ or electrons is known as reduction.

Biological oxidation : The oxidation in the living tissue cells is called biological oxidation.

Characteristics of biological oxidation :

i. It is the step wise degradation of metabolites for the generation of energy.

2. Final phase of biological oxidation is the utilization of O_2 and production of CO_2 by the tissues in the process of cellular respiration.

3. Enzymes, co-cnzymes and co-factors are needed for biological oxidation.

4. Enzymes of biological oxidation are highly specific, but co-enzymes & co-factors are not specific for a reaction.

The enzymic actions are activated by the presence of some accessory substances. When these accessory substances are single ions (Mg^+, PO_4^-), they are called *co-factors*, but when they are complex non-protein organic molecules, they are known as *co-enzymes*.

Difference between oxidation and biological oxidation :

Oxidation occurs only one step of reaction but biological oxidation occurs through several steps of reaction.

Oxido-reductases

Enzymes of biological oxidation :

Enzymes that carry out biological oxidation are known as oxido-reductases. They are classified into five groups.

1. *Oxidase :* They catalyses the removal of H_2 but uses only O_2 as hydrogen acceptor.
   Example : Cytochrome oxidase. phenolase, lactase etc.
2. *Aerobic dehydrogenase :* They catalyses the removal of H_2 but uses either O_2 or methyle blue, (artificial substances) as hydrogen aceptor.
   Example : D-amino-acid oxidase, L-amino-acid oxidase
3. *Anaerobic dehydrogenase :* They catalyses the removal of hydrogen but can not use O_2 as hydrogen acceptor.
4. *Hydroperoxidase :* These enzymes use H_2O_2 as their substrate.
5. *Oxygenase :* They catalyzes the direct transfer and incorporation of oxygen into substrate molecule.

Respiratory chain (electron transport chain) :

Respiratory chain is a series of catalyst in the inner mitochondrial membrane that are involved in the transport of reducing equivalents- H^+ or electron from the substrate to molecular oxygen to form water with the generation of ATP.

Organization (components) : There are four classes of components :

1. Flavoproteins (containing FMN & FAD)
2. Ubiquinone (coenzyme Q)
3. Iron-sulfur protein (FeS)
4. Cytochromes (cyt a, b, c).

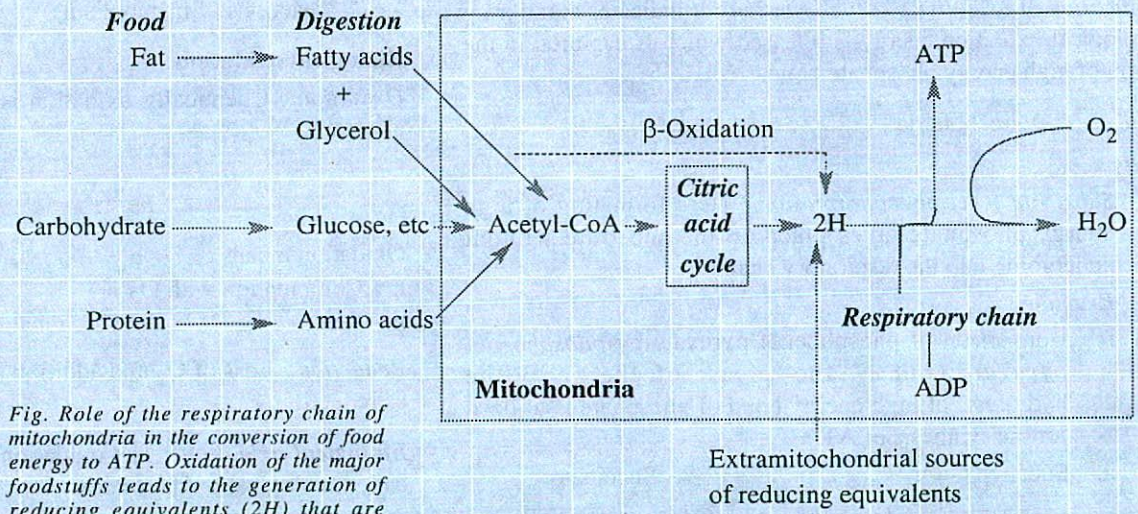


Fig. Role of the respiratory chain of mitochondria in the conversion of food energy to ATP. Oxidation of the major foodstuffs leads to the generation of reducing equivalents (2H) that are collected by the respiratory chain for oxidation and coupled generation of ATP.

(Ref: Harper's Illustrated Biochemistry 26th Edition, Page-93)

The components of the chain constitute five seperate protein-lipid respiratory chain complexes (complex I, 11, III, IV & V).

Cytochrome c is the only soluble cytochrome and together with *co-enzyme Q*, seems to be a more mobile component of the respiratory chain connecting the fixed complexes. Co-enzyme Q transports electron from the complexes I & II to complex III; cytochrome c transports electron from complex III to complex IV.

(Ref: Harper's Illustrated Biochemistry 26th Edition; Page-92)

Sites of ATP production :

i.	NAD	FMN
ii.	Cyt b	Cyt c_1
iii.	Cyt a	Cyt a_3

Importance :

The carriers in the respiratory chain are arranged so that spontaneous flow of electrons to oxygen is ensured. This is important to release energy by electron flow through respiratory chain.

Electron transport from NADH to oxygen produce 3 moles of ATP.

Respiratory chain co-enzymes : *Respiratory chain co- enzymes are* :

1. *FMN (flabin mononucleotide) & FAD (flabin adenine dinucleotide)* : These are the biologically active form of riboflavin (vitamin B_2).

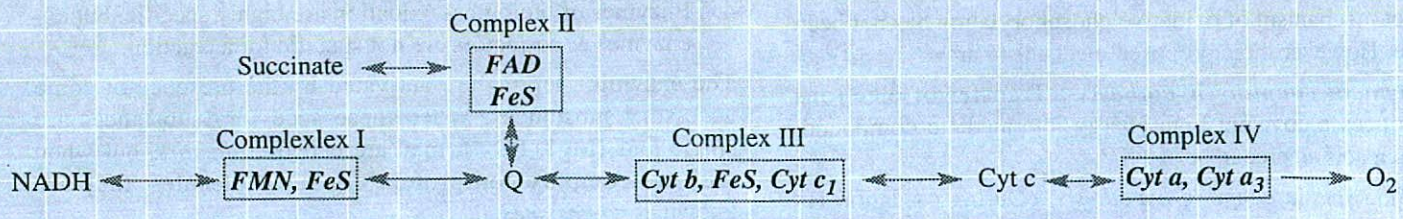


Fig: The respiratory chain complexes.

(Ref: Harper's Illustrated Biochemistry 26th Edition, Page-96)

Function of FMN :

a. FMN is bound to complex I and accepts 2 hydrogen atoms becoming $FMNH_2$.

b. FAD is bound to complex II and accepts 2 hydrogen atoms becoming $FADH_2$.

2. *Co-enzyme Q* : It is a quinone derivative with a long isoprenoid tail. It is also called ubiquinone because it is ubiquitous in biological systems.

   Function : It collects the reducing equivalents from the more fixed Fp complexes to the cytochromes.

3. *Iron-sulfur protein (FeS)* : It is an additional component in respiratory chain. It is nonheme iron.

   Function : It is associated with Fp (metallo-Fp) & with cytochrome b. The sulfur & iron take part in oxidoreduction between flavin &co-enzyme Q which involves a single e^- change, the Fe atom undergoing oxidoreduction between Fe^{++} & Fe^{+++}.

4. *Cytochromes* : They are the heam containing proteins. They act as e^- carriers in the respiratory chain. They are of 5 types :
   i. Cyt b
   ii. Cyt c_1
   iii. Cyt c
   iv. Cyt a
   v. Cyt a_3.

   Function : These cytochromes take part in electron transport between Fe^{++} & Fe^{+++}.

(Ref: Harper's Illustrated Biochemistry 26th Edition; Lippincott's Illuetrated Reviews of Biochemistry 23rd Edition)

Arrangement of the components of respiratory chain : The components of the respiratory chain are arranged in order to increasing redox potential.

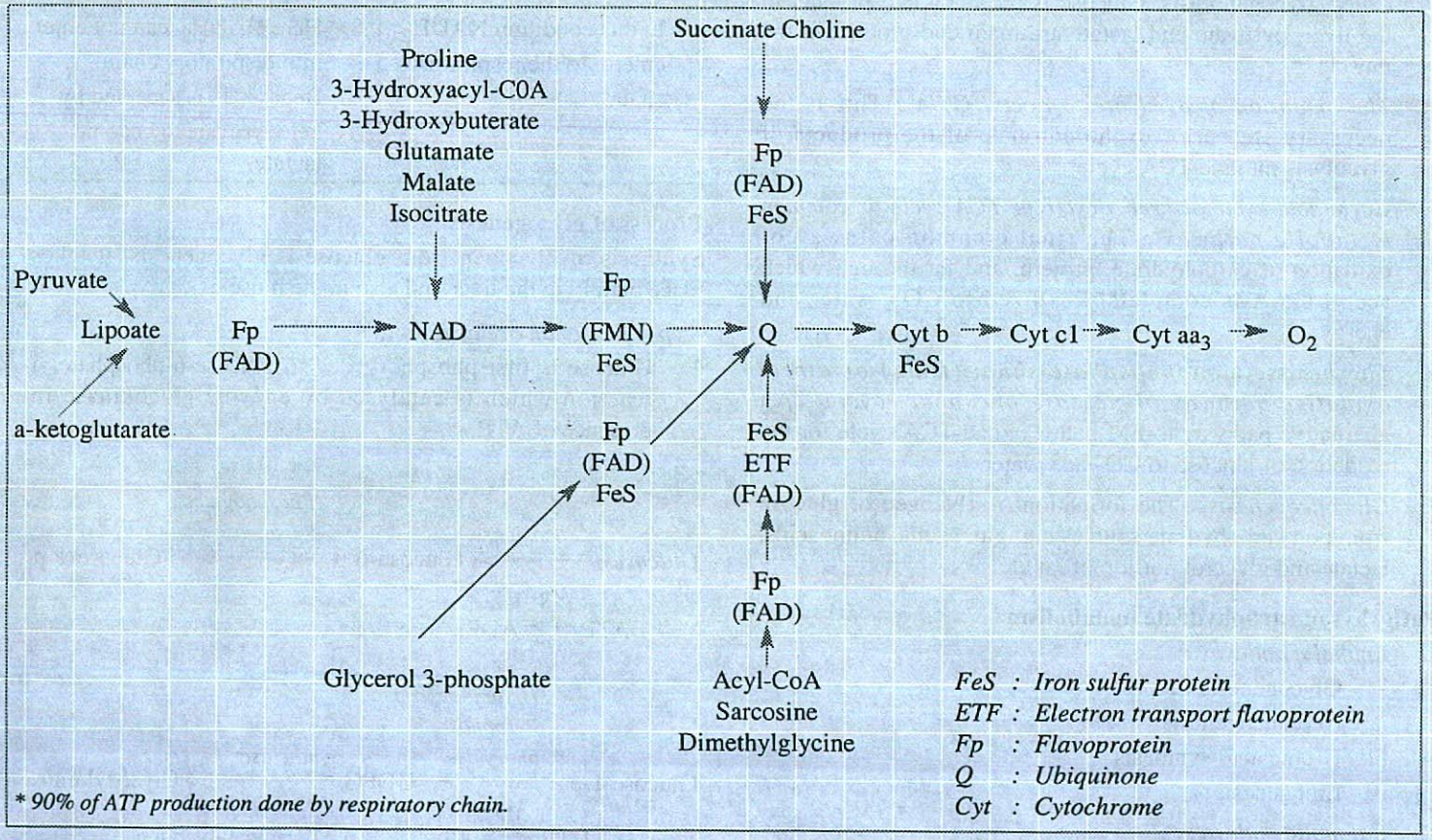


Fig. Components of the respiratory chain in mitochondria, showing the collecting points for reducing equivalents from important substrates. FeS occurs in the sequences on the O_2 side of Fp or Cyt b. *(Ref: Harper's Illustrated Biochemistry 26th Edition, Page-94)*

Carbohydrate Metabolism

The end products of carbohydrate digestion are mainly glucose (80%) and small amount of fructose and galactose. Galactose is converted exclusively in liver into glucose; fructose is converted both in the liver and muscles into glucose. So, glucose is the main form in which carbohydrate is metabolized in the body.

(Ref. Guyton & Hall 11th edition & Wright's)

Intermediary metabolism of carbohydrate : Intermediary metabolism of carbohydrate may be subdivided as follows :

1. *Glycolysis :* The oxidation of glucose to pyruvate or lactate by Embden-Meherhop pathway (EM).
2. *Glycogenesis :* Synthesis of glycogen from glucose is called glycogenesis.
3. *Glycogenolysis :* Breakdown of glycogen into glucose is called glycogenolysis. Glucose is the main end product in the liver, pyruvate and lactate are main end product in the muscle.
4. *The oxidation of pyruvate to acetyl Co-A :* This is the necessary step prior to the entrance of the products of glycolysis into the TCA cycle.
5. *Citric acid cycle or kreb's cycle or TCA cycle or common metabolic pathway :* The final common pathway of oxidation of carbohydrate, protein, and fat through which acetyl Co-A is completely oxdized to CO_2, water and energy.
6. *The hexose monophosphate shunt (HMS) or direct oxidative pathway or pentose phosphate cycle :* An alternative pathway to EM pathway and TCA cycle for the oxidation of glucose to CO_2 and water.
7. *Gluconeogenesis :* The formation of glycogen or glucose from non carbohydrate sources e.g. glucogenic aminoacids, lactate and glycerol portion of fat etc.

Pathways of carbohydrate metabolism

a. *Anabolic pathway :*
   i. Glycogenesis
   ii. Neoglucogenesis
   iii. Uronic acid synthesis
   iv. Lipogenesis.

b. *Catabolic pathway :*
   i. Glycolysis
   ii. Oxidation of pyruvate to acetyl CoA
   iii. TCA cycle
   iv. Glycogenolysis
   v. HMP shunt.

Q. ***Which metabolism gives more ATP and why?***

Ans. Aerobic pathway of carbohydrate metabolism give more ATP than anaerobic pathway. Because during aerobic pathway the $NADH_2$ enter into respiratory chain and oxidized. So, aerobic pathway give more ATP than anaerobic pathway.

Aerobic glycolysis

Breakdown of glucose in presence of oxygen is known as aerobic glycolysis.

Anaerobic glycolysis

Breakdown of glucose in absence of oxygen is known as anaerobic glycolysis.

Difference between aerobic and anaerobic glycolysis

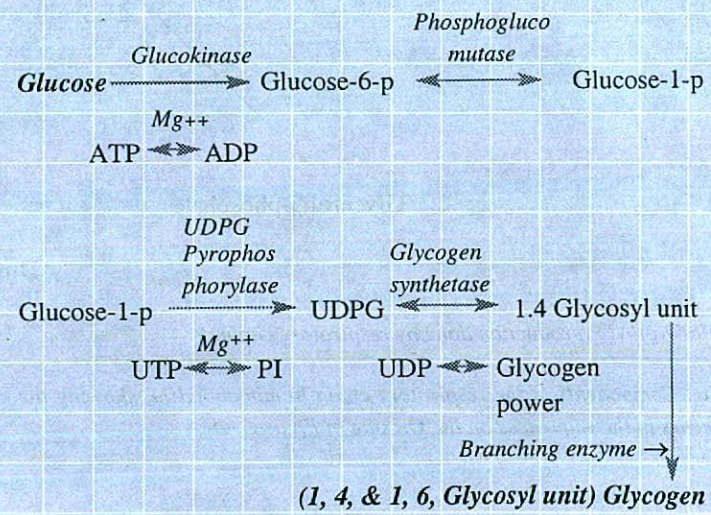
Aerobic	*Anaerobic*
1. In this condition pyru vate enters into the TCA cycle for oxidation.	1. In this condition pyruvate is converted into lactate in presence of lactatedehydro genase.
2. Here 8 molecules of ATP is formed.	2. Here 2 molecules of ATP is formed.
3. In this condition $NADH_2$ enter into the respiratory chain.	3. Here $NADH_2$ can not enter into respiratory chain. Becuse H^+ is accepted by ketopyruvate to become lactate.

Process of glycogenesis

Synthesis of glycogen from glucose is glycogenesis. It takes place mainly in the liver and also in the muscle.

Steps of reaction are as follows :

1. Glucose is first phosphorylated to glucose-6-phosphate, a reaction which is catalysed by enzyme glucokinase in presence of ATP.



2. Glucose-6-phosphate is then converted into glucose-1-phosphate, catalysed by the enzyme phosphoglucomutase.
3. Next glucose-1 phosphate reacts with urindine triphosphate (UTP) to form the active nucleotide uridine diphosphate

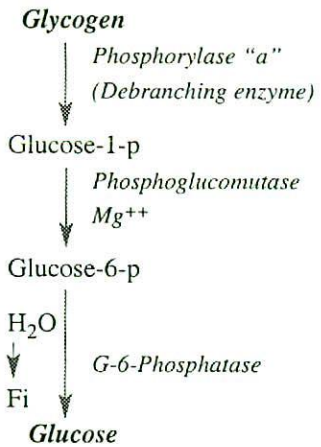
glucose (UDPG). This reaction is catalysed by enzyme UDPG pyrophosphorylase.

4. By the action of glycogen synthetase, the C_1 of the activated glucose of UDPG forms a glycosidic bond with C_4 of a non-reducing terminal glucose residue of pre-existing glycogen. Thus uridine diphosphate (UDP) is liberated.
5. A second enzyme called branching enzyme (amylo 1-4 & 1-6 transglucosidase) acts on glycogen and transfer a part of 1-4 chain of a neighbouring chain to form a 1-6 linkage and helps in glycogen synthesis by establishing a branch point in the molecule.

(Ref: Harper's Illustrated Biochemistry 26th Edition, Page-145)

Glycogenolysis

The process of breakdown of glycogen to reform glucose is known as glycogenolysis.



Steps of glycogenolysis : This takes place under the influence of an enzyme called phosphorylase. Phosphorylase exists in an inactive form phosphorylase "b" *(dephosphophosphorylase)*. It is activated to phosphorylase "a" (activated form) by the action of some hormones in the following way :

Epinephrine activates adenyl cyclase → Which causes the formation of cylic AMP → Which activates protein kinase regulator protein → Which activates protein kinase →Which activates phosphorylase b kinase → Which converts phosphorylase "b" into phosphorylase "a". This phosphorylase "a" promotes degradation of glycogen and the process of glycogenolysis proceeds in the following way :

a. The activatd phosphorylase (Phosphorylase "a") acts on glycogen and converts into glucose-1-phosphate.
b. The glucose-1-phosphate is converted into glucose-6-phosphate catalysed by the enzyme phosphoglucomutase.
c. In liver and kidney (but not in muscle) glucose-6-phosphate is converted into glucose under the enzymatic action of glucose-6-phosphatase. This glucose then passes into the blood.

(Ref: Harper's Illustrated Biochemistry 26th Edition, Page-145)

Glycolysis *(under aerobic condition)*

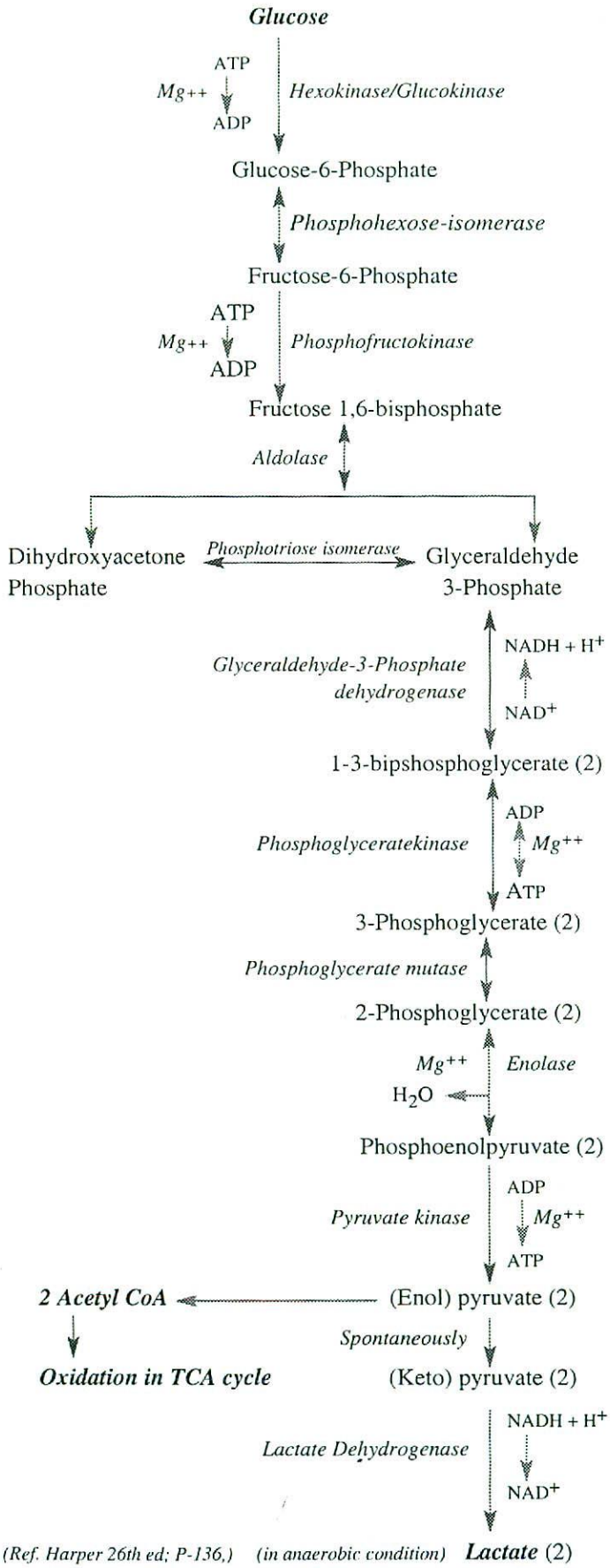
Gycolysis means oxidation of glucose or glycogen to pyruvate or lactate by Embden-meherhop pathway. It occurs in cytoplasm not in the nucleus or mitochondria.

Factors in glycolysis :

1. Substrate : Glucose
   i. Aerobic glycolysis : Pyruvate (2)
   ii. Anaerobic glycolysis : Lactate
2. Site : Allmost all cell
3. Compartment : Cytoplasm
4. Nature of pathway : Catabolic.

Steps of reaction :

1. Glucose is phosphorylated to glucose-6-phosphate. This is accomplished by the enzyme hexokinase and by an additional enzyme in the liver called glucokinase. ATP is required as phosphate donar and Mg^{++} acts as a co-factor and reacts as Mg-ATP complex. One high energy phosphate bond of ATP is utilized and ADP is produced.
2. Glucose-6-phosphate is converted to fructose-6-phosphate by phospho-hexose isomerase.
3. Fructose-6-phosphate is phosphorylated to fructose-1-6 bisphosphate, catalysed by the enzyme phosphofructo-kinase. ATP and Mg^{++} is required for phosphorylation.
4. Fructose 1-6-bisphosphate is split by aldolase into two triose phosphate- glyceraldehyd-3-phosphate and dihydroxy-acetone phosphate. These two triose phosphate are interconverted by the enzyme phosphotriose isomerase.
5. Glyceraldehyde-3 phosphate is then oxidized by glyceraldehyde-3 phosphate dehydrogenase into 1-3 diphosphoglycerate and because of the activity of the 6-phosphotriose isomerase the dihydroxyaectone phosphate is also oxidized to 1-3 diphosphoglycerate and glyceraldehyde 3 phosphate. Here removal of H^+ occurs which is accepted by NAD.
6. 1-3 diphosphoglycerate then denotes one high energy phosphate to ADP to convert it into ATP and it itself is transformed into 3 phosphoglycerate. This reaction is catalysed by phosphoglycerate kinase. Here Mg^{++} acts as a co-factor.
7. 3-phosphoglycerate is converted to 2-phosphoglycerate by the enzyme phosphoglycerate mutase.
8. 2-phosphoglycerate is convert to phosphoenol pyruvate by lossing 1-molecule of water (Dehydration). This reaction is catalysed by the enzyme enolase.
9. Phosphoenol pyruvate is converted into enolpyruvate by *pyruvatekinase*. In this reaction phosphoenolpyruvate losses PO_4 group which is accepted by ADP.
10. Then enolpyruvate spontaneously converted into ketopyruvate. This is another nonequilibrium reaction that



is accompanied by considerable loss of free energy as heat and must be regarded as physiologically irreversible.

Under aerobic conditions, pyruvate is taken up into mitochondria, and after conversion to acetyl-CoA is oxidized to CO_2 by the citric acid cycle.

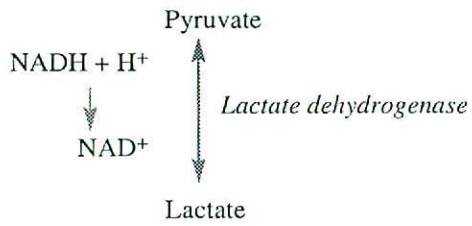
(Ref. Harper 26th ed; page-136, 137)

Glycolysis under anerobic condition

(Anaerobic pathway for carbohydrate metabolism) :

See steps of aerobic glycolysis and then add the following paragraph : In anaerobic conditions, the reoxidation of NADH by transfer of reducing equivalents through the respiratory chain to oxygen is prevented. Pyruvate, which is the normal end product of glycolysis under aerobic condition is reduced under anaerobic condition to lactate by NADH, the reaction being catalysed by "*lactate dehydrogenase*".

The reoxidation of NADH via lactate fromation allows glycolysis to proceed in the absence of oxygen by regenerating sufficient NAD^+ for the reaction catalysed by *glyceraldehyde-3-phosphate dehydrogenase.*



2 molecules of ATP is formed by glycolytic pathway under anaerobic condition.

N.B. In RBC : Always anaerobic glycolysis.

(Ref. Harper's 26th ed; page-139)

Q. ***How many ATP is formed during glycolysis under aerobic condition..***

Ans. 8 ATP is formed in glycolytic pathway under areobic condition. The following reactions are involved in the formation of ATP.

ATP used in glycolytic pathway :

Reaction catalyzed by	*Mechanism*	*Molecules of ATP*
1. Hexokinase/ Glucokinase.	At substrate level	1 ATP
2. Phosphofructo-kinase	At substrate level	1 ATP
		Total = 2 ATP

ATP gained in glycolytic pathway :

Enzymatic level	*Mechanism*	*Molecules of ATP*
1. Glyceraldehyde -3-phosphate dehydrogenase	Respiratory chain oxidation of 2 NADH	6 ATP

2. Phosphoglycerate kinase	Phosphorilation at substrate level	2 ATP
3. Pyruvate kinase	Phosphorilation at substrate level	2 ATP
	Total	= 10 ATP

So, ATP formed in aerobic glycolysis (10 - 2) = 8 molecules.

Q. ***How many ATP will formed from one mole of glucose in glycogen by glycolytic pathway?***

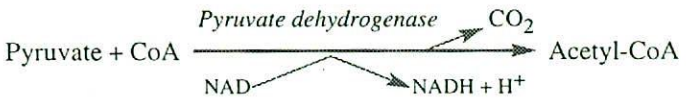
Ans.

3 moles of ATP will produced anaerobically from 1 mole of glucose in glycogen by glycolytic pathway. Because free glucose entering into the cell must be phosphorylated by 1 mole of ATP before it can begin to be split. Where as this is not true to glucose derieved from glycogen because it comes from glycogen in phosphorylated state without the expenditure of ATP.

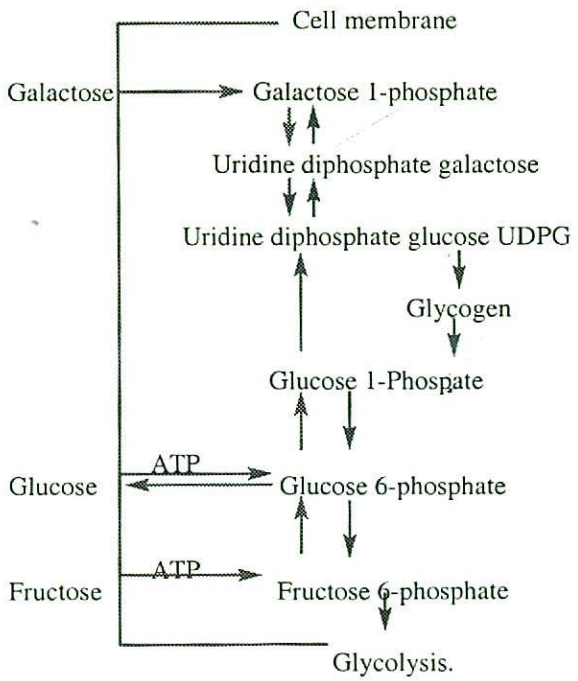
(Ref. Guyton & Hall 11th edition)

Q. ***How pyruvate is converted into Acetyl-CoA?***

Ans. Before pyruvate can enter the cytric acid cycle it must under goes oxidative decarboxylation to form acetyl-CoA. This reaction is catalysed by several enzymes collectively designated as *"pyruvate dehydrogenase complex"*.



Interconversion of glucose, fructose and galactose



(Ref. Guyton & Hall 11th edition)

Pyruvate

Source of pyruvate :

i. From glucose by glycolytic pathway
ii. From amino acid by transamination.
iii. From fatty acid by beta-oxidation.

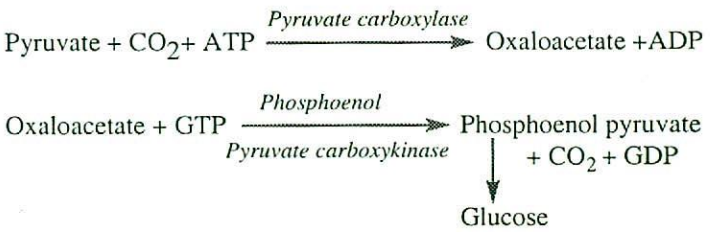
Fates of pyruvate : Pyruvate is converted into-

i. Lactic acid under anaerobic condition.
ii. Acetyl CoA by oxidative decarboxylation.
iii. Oxaloacetic acid by carboxylation.
iv. Glucose in TCA cycle by gluconeogenesis
v. Alanine by transamination.

Q. ***How pyruvate is converted into glucose?***

Ans. Pyruvate is converted into glucose by gluconeogenesis reaction.

i. An enzyme pyruvate carboxylase in presence of ATP, biotin and CO_2 converts pyruvate to oxaloacetate, it occurs in mitochondria.
ii. Second enzyme "phosphoenol pyruvate carboxykinase" catalyses the convertion of oxaloacetate to phosphoenol pyruvate. High energy phosphate in the form of GTP is required and CO_2 is liberated.
iii. Phosphoenol pyruvate then converted into glucose by series of reactions.

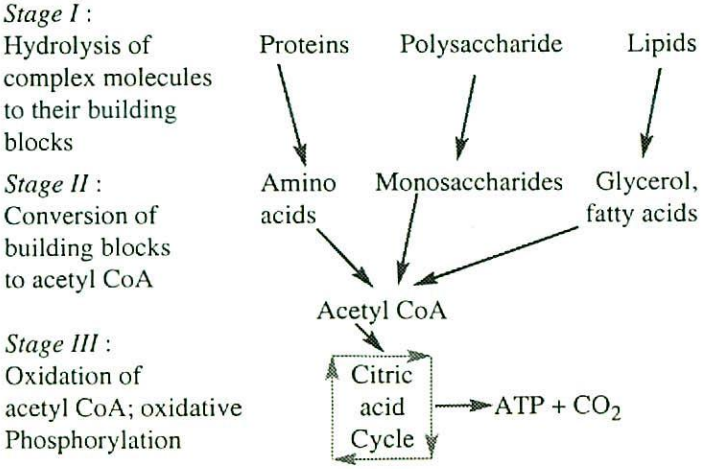


(Ref. Harper's 26th edition)

Source and fate of acetyl CoA

Source :

i. Carbohydrate metabolism (Glycolysis).
ii. Fat metabolism (Beta-oxidation).
iii. Protein metabolism (Transamination).



(Ref. Lippincott's Illustrated Reviews 3rd Edition)

Fate of acetyl-CoA :

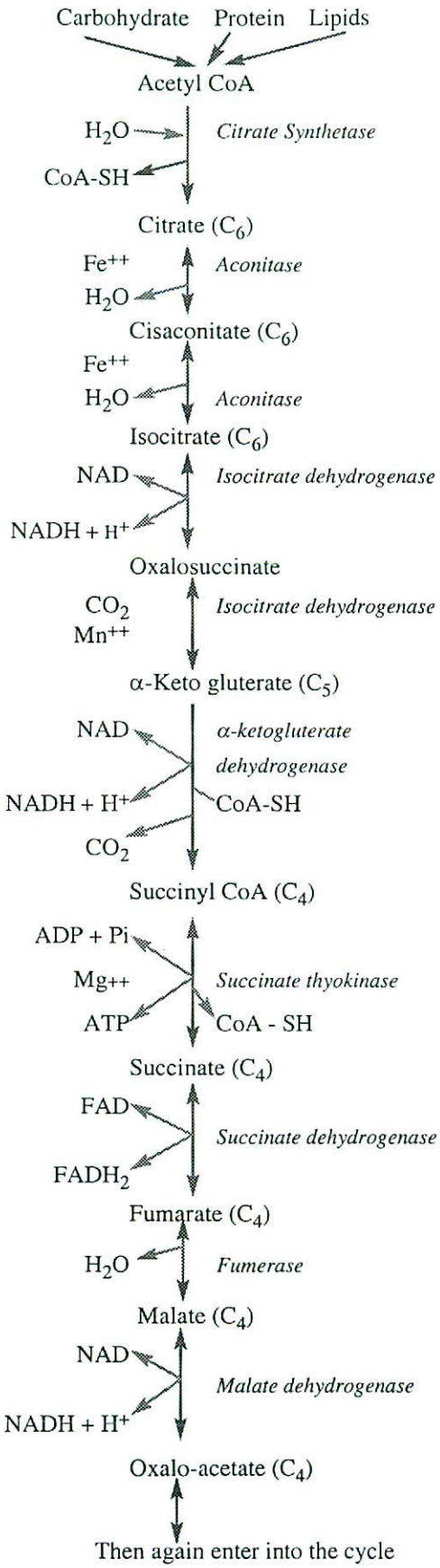
a. Utilization in TCA cycle to produce CO_2, water and energy.
b. Acetyl CoA gives rise to cholesterol synthesis.
c. Acetyl CoA gives rise to fatty acid synthesis.
d. Formation of ketone bodies.
e. Synthesis of steroid substances.
f. Acetyl CoA undergoes acetylation reactions.

TCA cycle

1. Substrate : CO_2, H_2O, energy
2. Site : Mitochondrial
3. Compartment : Mitochondria
4. Nature of pathway : Amphibolic.
5. *ATP production from 1 mole of glucose* :
   - i. Glycolysis : 8 ATP (10-2)
   - ii. 2 Pyruvate to 2 acetyl CoA : 6 ATP
   - iii. TCA cycle (2 acetyl CoA) : 24 ATP (12x2)
   - *Total* = *38 ATP*

Reactions of the citric acid cycle : Before pyruvate can enter the TCA cycle it must undergo oxidative decarboxylation to form acetyl-CoA with the help of pyruate dehydrogenase complex.

1. *Condensation* : The acetyl-CoA condenses with oxaloacetate to form citrate, a reaction catalyzed by a condensing enzyme citrate synthetase. This is the first reaction of citric acid cycle.
2. *Dehydration and rehydration* : Citrate first by a process of dehydration is converted into cisaconitate. Which again by a process of rehydrations transformed into isocitrate. The enzyme aconitase catalyzes both the steps.
3. *Dehydrogenation* : Isocitrate undergoes dehydrogenation in presence of isocitrate dehydrogenase to form oxalosuccinate. NAD acts as hydrogen acceptor and converted into $NADH_2$.
4. *Decarboxylation* : An enzyme isocitrate dehydrogenase in presence of Mn^{++} removes CO_2 from oxalosuccinate which is thus converted into α-ketogluterate.
5. *Oxidative decarboxylation* : Next α-ketogluterate under goes oxidative decarboxylation and converted into succinyl CoA. This reaction is catalyzed by α- ketogluterate dehydrogenase complex.
6. *Succinyl CoA* is converted into succinate by the enzyme succinate thiokinase (Succinyl CoA synthetase). This reaction require GDP or IDP which is converted in presence of inorganic phosphate (IP) to GTP or ITP.
7. *Dehydrogenation* : Succinate is converted into fumerate by succinate dehydrogenase. The hydrogen is transfered directly to FAD-converting it into $FADH_2$.



(Ref. Harper 26th edition; page-130, 131)

8. *Hydration* : Under the influence of fumarase water is aded to fumerate and converted it into malate.
9. *Dehydrogenase* : By this process malate is converted into oxaloacetate by malate dehydrogenase, a reaction requiring NAD^+. Oxaloacetate then again enter into the cycle.

(Ref. Harper's 26th ed; page 130)

Q. ***How many ATP is formed in citric acid cycle?***

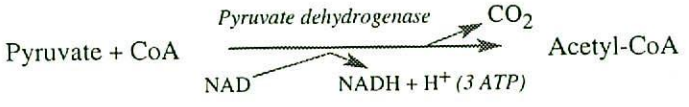
Ans.

TCA Cycle starts from Acetyl-CoA and one molecule of Acetyl CoA forms 12 molecule of ATP. They are formed in the following way :

Reaction catalyzed by	*Method of high-energy p production*	*Number of high-energy p formed per molecule of glucoes*
1. Isocitrate dehydrogenase	Respiratory chain oxidation of NADH	3
2. α ketogluterate dehydrogenase	Respiratory chain oxidation of NADH	3
3. Succinate thiokinase	Phosphorylation at substrate level	1
4. Succinate dehydrogenase	Respiratory chain oxidation of $FADH_2$	2
5. Malate dehydrogenase	Respiratory chain oxidation of NADH	3
		Net = 12 ATP

ATP formed in TCA cycle :

1. From Acetyl CoA (1) : 12 ATP.
2. From pyruvate (1) : 15 ATP (3 ATP + 12 ATP)



(Ref. Harper's 26th edition, page-133)

Generation of high-energy phosphate in the catabolism of glucose :

A. ***Glycolysis*** :

ATP used in glycolytic pathway :

Reaction catalyzed by	*Method of high-energy p production*	*Number of high-energy p used per molecule of glucoes*
1. Hexokinase/ Glucokinase.	At substrate level	1 ATP
2. Phosphofructo-kinase	At substrate level	1 ATP
		Total = 2 ATP

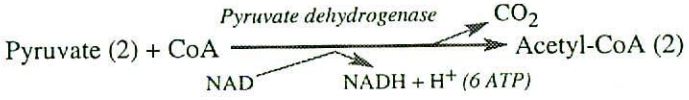
ATP gained in glycolytic pathway :

Reaction catalyzed by	*Method of high-energy p production*	*Number of high-energy p formed per molecule of glucoes*
1. (2) Glyceraldehyde -3-phosphate dehydrogenase	Respiratory chain oxidation of 2NADH	6 ATP
2. Phosphoglycerate kinase	Phosphorilation at substrate level	2 ATP
3. Pyruvate kinase	Phosphorilation at substrate level	2 ATP
Total		= 10 ATP

So, In aerobic glycolysis : (10 - 2) 8 molecules of ATP + 2 molecules of pyruvate is formed.

B. ***Citric acid cycle*** :

(1 molecule of glucose = 2 pyruvate = 2 Acetyl CoA)



Reaction catalyzed by	*Method of high-energy p production*	*Number of high-energy p formed per molecule of glucoes*
1. Pyruvate dehydro genase	Respiratory chain oxidation of *2 NADH*	6
2. Isocitrate dehydro genase	Respiratory chain oxidation of *2 NADH*	6
3. α-ketogluterate dehydrogenase	Respiratory chain oxidation of *2 NADH*	6
4. Succinate thiokinase	Phosphorylation at substrate level	2
5. Succinate dehydrogenase	Respiratory chain oxidation of *2* $FADH_2$	4
6. Malate dehydrogenase	Respiratory chain oxidation of *2 NADH*	6
		Net = 30

Total per mole of glucose under aerobic conditions : 38 (8+30)
Total per mole of glucose under anaerobic conditions : 2

(Ref. Harper's 26th edition; Page 143)

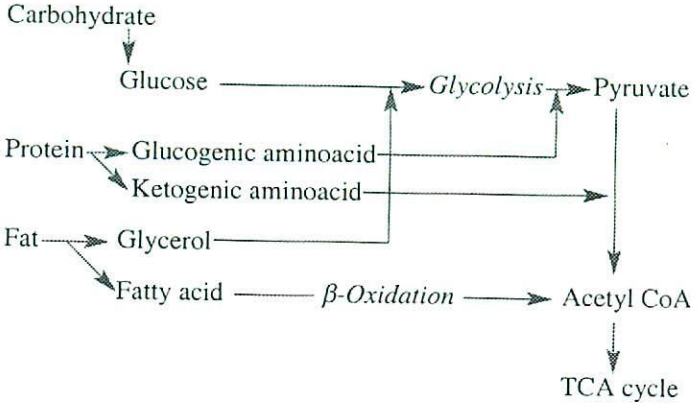
Q. ***Show diagramatically and explain that TCA cycle is the common metabolic pathway.***

Ans. *Explanation* :

1. Glucose formed by carbohydrate digestion is undrgone through EM pathway and form pyruvic acid (Ketoacid) which then form acetyl CoA by oxidative decarboxilation reaction.

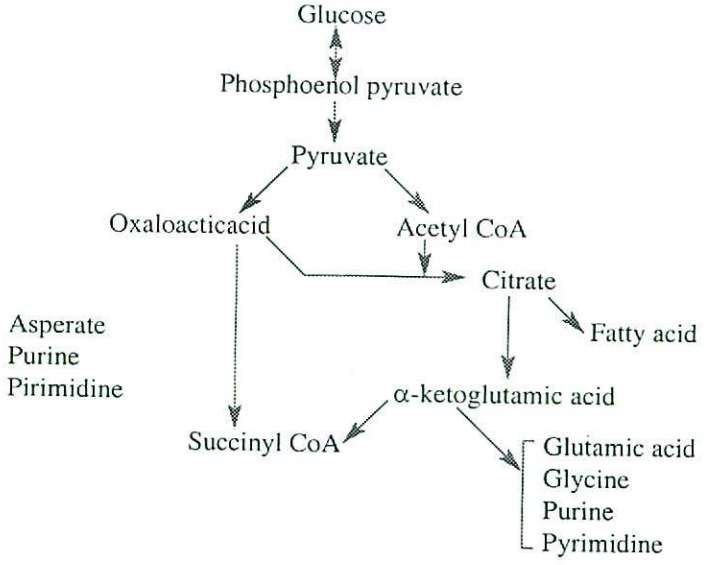
2. Amino acid, comes from hydrolysis of protein, passes through deamination and transamination and form keto acid. This keto acid then form acetyl Co-A.

Table : TCA cycle as common metabolic pathway :



3. Fatty acid, formed by the digestion of fat, enters into beta-oxidation and form acetyl Co-A.
4. Acetyl CoA comes from the metabolism of carbohydrate, protein and fat; then couples with oxaloacetic acid and initiate TCA cycle.

TCA cycle as amphibolic (catabolic + anabolic) :



HMP-shunt

Hexose monophosphate shunt pathway is an alternative pathway to Embden-Meherhop pathway and citric acid cycle for the oxidation of glucose to CO_2 and water. It is called hexose monophosphate shunt because it strarts from glucose-6-phosphate and all the reaction is phosphate related.

Importance of HMP-shunt :

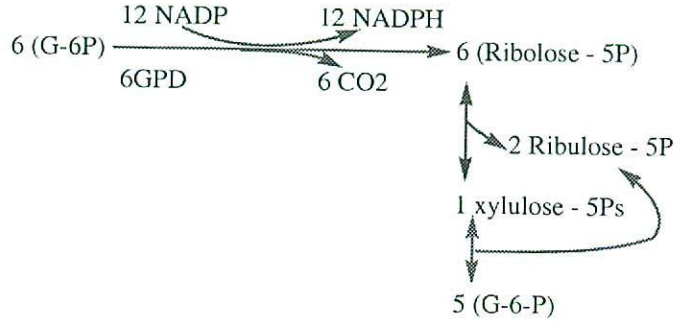
1. To produce ribose for nucleotide synthesis
2. To produce NADPH for-
   i. Reductive synthesis of fatty acid, steroid, cholesterol
   ii. Detoxifing function of liver
   iii. Anti-oxidant activity
   iv. Bacterial killing in phagocytosis
3. Alternate pathway for glucose oxidation.

Factors of HMP-shunt :

i. Site : Cytosol

ii. 10% of body glucose is oxidised by HMP-shunt.

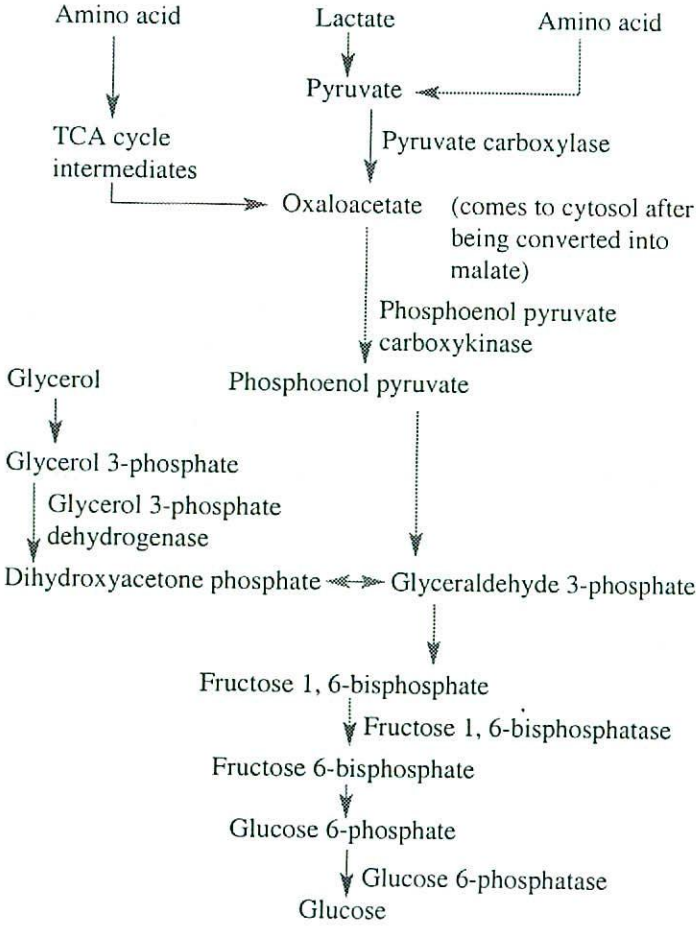
iii. Steps :



Neoglucogenesis / gluconeogenesis

Definition : The formation of glycogen or glucose from non carbohydrate sources e.g. glucogenic aminoacids, lactate and glycerol portion of fat etc.

Steps of gluconeogenesis :



Factors of gluconeogenesis :

1. Substrate : Glucogenic aminoacid, glycerol, lactate, pyruvate, intermediates of TCA cycle.
2. Product : Glucose
2. Site : Liver (90% of total), kidney (10% of total)
3. Compartment : Primarily cytoplasm
4. Nature of pathway : Anabolic.

Most important substrate of neoglucogenesis is glucogenic aminoacids.

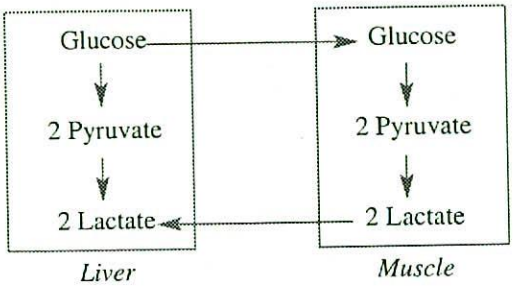
Biomedical importance :

1. To fulfill the need of glucose of the body because every cell needs a particular amount of basal glucose to maintain TCA cycle.
2. Some tissues & cells are solely dependant on glucose. Gluconeogenesis supports the supply of glucose to these obligate glucose consuming cells - neurons, RBC, renal medulla & gonads.
3. Maintenance of blood glucose concentration during fasting and starvation & in between meals.

Oxaloacetatc is the key intermediate of gluconeogenesis because it is the final intermediate of TCA cycle that can be converted to glucose by gluconeogenesis.

Cori cycle or *lactic acid cycle*

Lactic acid produced in the muscle reaches the liver through blood, where it is converted into glucose by gluconeogenesis, which again becomes the source of energy for utilization. Thus this continues and is called " Coti cycle or lactic acid cycle."



Lactate disposal :

i. Lactate production : 750-1500 meq/day
ii. Lactate disposal : Mostly by cori-cycle.

Sources of blood glucose

There are two important sources, which give rise to glucose in the body :

1. *Dietary source :* Carbohydrates of food after digestion and absorption are the chief source.
2. *Sources within the body :*
   a. Glycogenic compound : Glycogenic amino acid, glycerol of fat & intermediate products of glycolytic pathway; by process of gluconeogenesis.
   b. Liver glycogen : By process of glycogenolysis.

End product of glucose :

1. In aerobic glycolysis : Pyruvate.
2. In anaerobic glycolysis : Lactate.

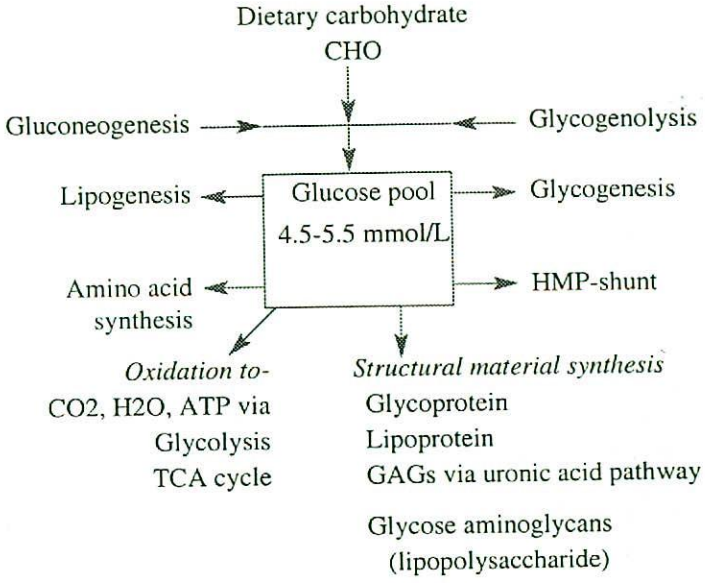
Fate of glucose :

Possible fates of glucose are as follows-

1. Provision of energy to body; About 4.1 kcal/gm.
2. Storage as glycogen in the liver and muscle.
3. Convertion into fat and stores in the fat depots.
4. Transamination of some intermediate products of glucose break down to form amino acid.

(Ref. Wright's)

Carbohydrate pool



Importance of glucose :

1. It is the major source of energy in the body.
2. Certain tissues like nervous tissues can utilize only carbohydrates (glucose).
3. It supplies energy to muscles even without the presence of O_2, when no other source of energy can be utilized.
4. It supplies raw materials for formation of milk suger in mammary gland.
5. It is lipogenic.
6. It is the chief source of high energy phosphate.

Sources of liver glycogen

The possible sources of liver glycogen are-

1. *From carbohydrate & related substances* :
   a. End products of carbohydrate digestion e.g. Glucose, fructose & galactose
   b. The intermediate products of carbohydrate metabolism e.g-Pyruvic acid, lactic acid etc.
2. *From Proteins* : The anti-ketogenic amino acid can readily form glucose through TCA cycle or reversible glycolytic pathway or both. These are-Glycine, alanine, aspartic acid, glutamic acid etc.

3. *From fats* : The glycerol part of fat is converted into glucose from which glycogen may be derived.

Fate of liver Glycogen :

1. It converts into glucose when blood glucose level tends to fall.
2. It break downs & liberates energy in starvation, exercise etc.

Source of muscle glycogen

1. Blood glucose
2. From lactic acid : Which is produced in the muscle during its contraction. The major part (4/5th) of lactic acid produced during exercise is reconverted into glycogen..

Fate of muscle glycogen :

It can only breaks down into lactic acid.

Q. ***Why muscle glycogen cannot be the source of blood glucose?***

Ans.

Muscle glycogen cannot be the source of blood glucose, because muscle lacks an enzyme glucose-6-phosphatase; necessary for conversion of glucose.

Q. ***How muscle glycogen is utilized for energy?***

Ans.

In glycogenolysis, the muscle glycogen is firstly converted into glucose-1-phosphate then glucose-6-phosphate. Since the muscle tissue contains no *glucose-6-phosphatase*, the glucose-6-phoshate converted into fructose-6-Phosphate which enters either the EM pathway or hexose monophosphate shunt pathway and utilized for energy, thus lactic acid is formd.

Difference between liver and muscle glycogen

Liver glycogen	*Muscle glycogen*
1. Amou nt : 100 mg	1. Amount : 400 mg
2. Liver glycogen is utilized for maintenance of blood sugar.	2. Muscle glycogen is not available for maintaining of blood sugar.
3. Turn over rate- rapid	3. Turn over rate slow.
4. As fuel not used by the liver.	4. Used by the muscle.
5. Source : From carbohydrate, lactic acid as well as muscle, from protein and fats.	5. Source : From blood glucose, muscle, lactic acid, not from proteins.
6. Liver glycogen can converted into glucose.	6. Muscle glycogen can not converted into glucose.
7. Glycogen breakdown is mostly upto glucose.	7. Glycogen breakdown is upto pyruvate and lactate.
8. Almost mobile.	8. Less mobile.

Q. ***Why CHO are stored in the form of glycogen?***

Ans. Glycogen is a suitable form to store carbohydrate because-

1. It is insoluble & so exerts no osmotic pressure.
2. It can not diffuse from its storage sites.
3. It is readily broken down to glucose in the liver to enter the blood stream.
4. It has a higher energy level than a corresponding weight of glucose.

(Ref. Wright's 13th page-451)

Glucostatic function of liver

Definition : Maintenance of normal blood glucose level by liver during the tendancy of hypoglycemia or hyperglycemia is called glucostatic function of liver.

I. *In hyperglycemia* :
   a. Increase glycogenesis
   b. Increase lipogenesis.

II. *In hypoglycaemia* :
   c. Increase glycogenolysis
   d. Increase gluconeogenesis.

Importance of glucostatic function :

1. Fuel supply to neuron and RBC
2. Minimum basal glucose supply to every cell
3. Prevent cerebral impairment
4 Prevent ketosis, (-) N_2 balance.

Mechanism :

a. *Glycogenolysis* : During fasting when both the blood concentration and insulin level fall, the liver releases glucose from its stored glycogen by the process of glycogenolysis. By this process, the liver can maintain normal blood glucose level upto 12-18 hours.
b. *Gluconeogenesis* : Liver can store 100 gm glycogen. In starvation, at least 12-18 hours after meal, all stored glycogen is broken down into glucose. Then gluconeogenesis starts ie. glucose is formed from non-carbohydrate substances. Thus normal blood glucose level is maintained.
c. *Glycogenesis* : After the ingestion of carbohydrate, when blood glucose level rises to a high level and insulin secretion increases, as much as is $^2/_3$ of glucose absorbed from the gut is stored immediately as glycogen in liver and muscle. Thus blood glucose concentration remains normal.
d. *Lipogenesis* : Extra glucose i.e if glucose in blood after 100 gm glycogen in liver and 400 gm glycogen in muscle which is their highest capacity of storage, is converted into fat by the process of lipogenesis.

Hypoglycaemia :

Blood glucose less than 55 mg%.

1. Fasting hypoglycaemia e.g in cirrhotic patient
2. Reactive or poestprandial- common.

Hypoglycaemia protection by :

i. Glucagon
ii. Cortisol
iii. Catecholamine
iv. Growth hormone.

Factors maintaining blood glucose level

1. Humoral
2. Hormonal
3. Nervous.

Humoral factors :

It includes :

i. Role of liver : The liver acts as an important *blood glucose buffer system.*
   a. When blood glucose level rises to very high, after a meal, 2/3 of glucose absorbed from gut is almost immediately stored in liver as glycogen.
   b. When blood glucose level falls, liver releases glucose back into blood due to presence of glucose-6-phosphatase.
   c. When glycogen reservoir diminishes, liver enhances gluconeogenesis.

ii. Role of muscle :
   a. During increase blood glucose level : Promotes glycogenesis and oxidation of glucose in muscle.
   b. During decrease blood glucose level : Muscle glycogen supplies glucose to blood by cori cycle. It can not serve as a direct source of blood glucose during hypoglycaemia due to absence of glucose-6-phosphatase.
   c. During exercise : It promotes entry of glucose into muscle cell thus decreasing blood glucose level.

iii. Role of kidney :
   a. During increase blood glucose level : When blood glucose level exceeds the renal threshold level, excess glucose is excreted in urine, thus decreases blood glucose level.
   b. During decrease blood glucose level : Kidney possesses gluconeogenesis, thus increases blood glucose level.

Hormonal factors :

i. Insulin : Decrease blood glucose level
   a. Increase glucose uptake from blood to all cells of the body
   b. Increase glycolysis
   c. Increase glycogenesis
   d. Decrease glycogenolysis
   e. Decrease gluconeogenesis

ii. Glucagon : *Increase blood glucose level*
   a. Increase glycogenolysis
   b. Increase gluconeogenesis

iii. Glucocorticoids : *Increase blood glucose level*
   a. It stimulates the gluconeogenesis in liver,
   b. It decreases the peripheral utilization of glucose.
   c. It decreases the transport of glucose to the periphery.

iv. Growth hormone : *Increase blood glucose level*
   a. Decrase uptake and utilization of glucose

v. Epinephrine : *Increase blood glucose level*
   a. Increase glycogenolysis

vi. Thyroid hormones : *Increase blood glucose level*
   a. Increase glycogenolysis
   b. Increase gluconeogenesis

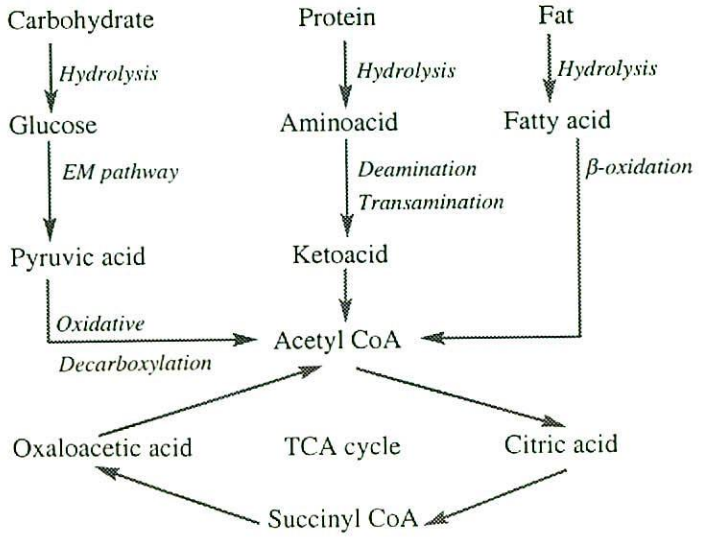
vii. ACTH : *Increase blood glucose level*
   a. Increase gluconeogenesis.

Nervous factor :

1. Hunger sensation : Raises blood glucose level by taking food during hypoglycemia.
2. Satiety : Inhibits hunger centre, there by decreases blood glucose.

N.B. *Neuron, RBC : 100% dependent for nutrition on glucose.*

TCA cycle as common metabolic pathway :



Protein metabolism

Definition : The metabolism of proteins means metabolism of amino acids.

Body can not produce essential amino acid from glucose but can do non-essential amino acid.

Factors f protein metabolism :

i. Protein turn over : 1-2% (300-400 gm/day) of the total body protein (12-14 kg).

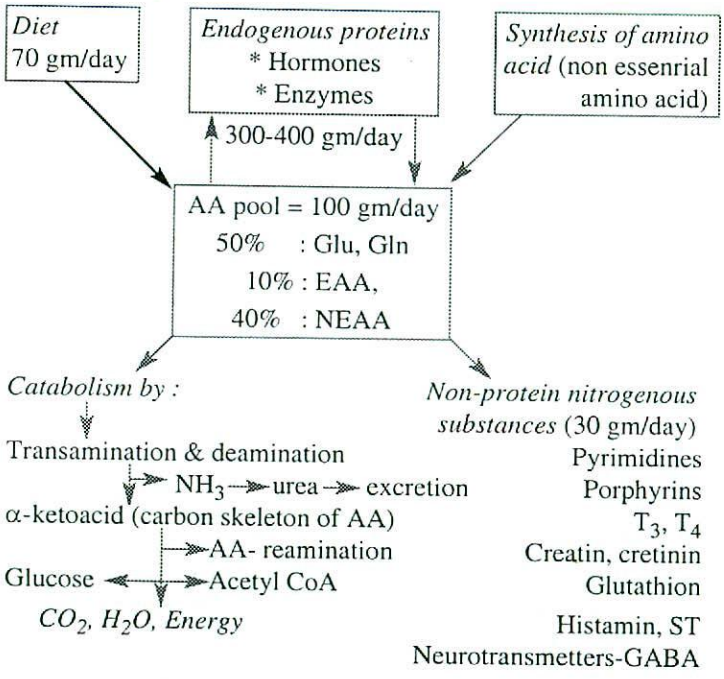
ii. Site : All cells of the body

iii. Compartment : Lysosomes

iv. Every amino acid converts to corresponding ketoacid by deamination.

v. Every ketoacid converts to corresponding amino acid by amination.

Amino acid pool :



Amino acid pool : There are constant exchange of amino acid from tissue to blood and other body fluids and reversely from body fluid to the tissue, which is known as amino acid pool. The inflow and out flow are so balanced that the dynamic equilibrium of amino acid is maintained nicely.

Inflow of amino acids into pool :

1. Amino acid from dietary proteins.
2. Break down of tissue protein.
3. Synthesis of amino acids by transamination of keto acids in the liver.
4. Reabsorption of amino acids from renal tubules.

Out flow of amino acids from the pool :

1. Synthesis of protein in the body.
2. Synthesis of essential non-protein nitrogen compound.
3. Synthesis of non-protein substances.
4. Oxidation to yeild energy.

Fate of amino acids :

By the process of deamination, amino acid is broken into two parts-

i. Nitrogenous parts

ii. Non-nitorgenous part.

i. ***Fate of nitrogenous part (ammonia)*** : Ammonia undergoes the follwing fates :
   1. Formation of urea.
   2. Formation of ammonium salts.
   3. Formation of new protein.
   4. It may be used for synthesis of various nitrogenous substances such as creatinine, purine, uric acid, lacithine etc.
   5. It may be excreted through urine.

ii. ***Fate of non-nitrogenous part*** : This part of amino-acid has the following fate-
   1. Helps in the formation of glucose by neoglucogenesis.
   2. Give rise to ketone bodies.
   3. Sulphur and phosphorus compounds are formed and are excreted.

Amino acids

1. ***Glucogenic amino acid*** :
   i. *Definition* : Amino acids whose catabolism yields pyruvate or one of the intermediates of the citric acid cycle are called glucogenic amino acids.
   ii. *Example* :
      a. *Essential glucogenic amino acids* : Arginine, histidine, methionine, threonine, valine.
      b. *Non-essential glucogenic amino acids* : Alanine, asparagine, asparate, cysteine, glutamate, glutamine, glycine, proline, serine.
2. ***Ketogenic amino acid*** :
   i. *Definition* : Amino acids whose catabolism yields either acetoacetate or one of its precursors- acetyl CoA or acetoacetyl CoA are called ketogenic amino acids.
   ii. *Example* :
      a. Essential ketogenic amino acids : Leucine, lysine.
3. ***Both glucogenic and ketogenic amino acid*** :
   i. *Definition* : Amino acids whose catabolism yields either pyruvate/one of the intermediates of the citric acid cycle or acetoacetate/one of its precursors- acetyl CoA/ acetoacetyl CoA are called both glucogenic and ketogenic amino acid.
   ii. *Example* :
      a. Essential both glucogenic and ketogenic amino acids : Isoleucin, phenylalanine, tryptophan

b. Non-ssential both glucogenic and ketogenic amino acids : Tyrosine.

(Lippincott's Illustrated Reviews of Biochemistry 2nd Edition; P 246)

Process of protein metabolism

Proteins are catabolized in the following ways :

i. Transamination.
ii. Oxidative deamination.
iii. Ammonia transport.
iv. Reactions of the urea cycle.

(Ref. Harper's 26th edition)

Transamination

Interconversion of a pair of amino acid and a pair of ketoacid. That is conversion of one amino acid to the corresponding ketoacid with simultaneous conversion of another keto acid to an amino acid is called transamination. In this reaction amino group of an amino acid is transfered to the keto group of ketoacid resulting in the formation of corresponding ketoacid and amino acid. This reaction is catalized by transaminase or aminotansferase enzyme. It is reversible.

Alanine + alpha ketogluteric acid $\xrightarrow{\text{Transaminase}}$ Pyruvic acid + Glutamic acid

(Ref. Harper's 26th edition)

Factors of transamination :

i. Compartment : Cytoplasm
ii. Sites : Liver, skeletam muscle, cardiac muscle
iii. Direction : Bi-direction
iv. Enzyme : Transaminase.
v. Amino acid : Any ketoacid can participate in transamination i.e-
   a. α-keto gluterate ⇢ Glutamate
   b. Pyruvate ⇢ Alanine
   c. Oxaloacetate ⇢ Asperate.

Importance of transamination :

1. This is an easy way of forming new amino acids (Non essential) from α-keto acids.
2. It provides a link between fat, carbohydrate and protein metabolism, as the keto acids come from the metabolic cycle.
3. It serves a missing link in the pathway of ammonia formation.
4. By this process-amino acids synthesized in the liver pass to the amino acid pool.

Oxidative deamination

Deamination means removal of amino group from an amino acid thus transforming it to the corresponding ketoacid. As oxidation occurs simultaneously by dehydrogenation, it is also called oxidative deamination. It occurs in the liver. Here amino acid oxidase is involved.

1. *Step.1 :* Amino acid is first dehydrogenated by amino acid oxidase to form imino acid. Hydrogen ions are carried by FAD and converted into $FADH_2$.
2. *Step.2 :* The iminoacid then spontaneously hydrolyzed to the corresponding ketoacid with liberation of ammonia.

Aminoacid (alanine)
FAD ↓ — *Aminoacid oxidase*
$FADH_2$ ↓
Iminoacid + H_2O
↓
Keto acid (pyruvic acid) + NH_3

Factors of oxidative deamination :

i. Compartment : Cytoplasm
ii. Sites : Liver and kidney
iii. Substrate : Amino acid
iv. Products : NH_3 and keto acid
iv. Enzyme : Amino acids oxidase, glutamate dehydrogenase

Importance :

i. Formation of NH_3 which serves as a source of nitrogen in urea synthesis.
ii. Formation of a-keto acid which can enters into the central pathway of urea synthesis.

(Ref. Harper 26th edition)

Fates of keto acid

The ketoacids resulting from deamination of amino acids are mostly oxidized with energy release. This oxidation involves conversion of keto acid into an intermediate product that enters into the TCA cycle and is degraded e.g ketoacid obtaining from alanine is pyruvic acid, obviously it can be cornverted into acetyl CoA and then into fatty acids. Also 2 molecules of aetyl CoA condense to form acetoacetic acid.

Fate of ammonia in the body

I. *Ammonia undergoes the follwing fates* :
   1. Formation of urea.
   2. Formation of ammonium salts.
   3. Formation of new protein.
   4. It may be used for synthesis of various nitrogenous substances such as creatinine, purine, uric acid, lacithine etc.
   5. It may be excreted through urine.

II. *Metabolic disposal of ammonia : Ammonia is disposed from the body mainly by 2 processes* :
   i. *By excreting NH_3* : Ammonia is secreted into the renal tubules derived from glutamine in the presence of glutaminase.

ii. *By forming urea* : The free ammonia which is produced in the body, circulated in the blood is taken up by the liver and converted into urea by urea cycle. Then it is excreted through the kidney into urine. Brain tissue can form urea but this does not play a significant role in ammonia removal.

Mechanism of synthesis of urea *or* urea cycle

Liver is the only site of the urea formation. The process of urea synthesis divided into five different phases.

1. *Synthesis of carbamyl phosphate* : Condensation of 1 molecule each of ammonia, CO_2 and phosphate (derived from ATP) forms carbamyl phosphate. This reaction is catalyzed by carbamyl phosphate synthetase. 2 molecules of ATP hydrolyzed during this reaction provide the driving force for synthesis of two covalent bonds-
   a. The amide bond.
   b. Mixed carboxylic acid-phosphoric acid anhydride bond.

   In addition Mg^{++} and a carboxylic acid, N-acetylglutamate is required.
2. *Synthesis of citruline* : Transfer of a carbamyl moiety from carbamyl phosphate to ornithine, forming citruline and Pi. This reaction is catalyzed by L-ornithine transcarbamylase of liver mitochondria.
3. *Synthesis of arginine succinate* : In this reaction aspartate and citruline are linked together via amino group of asparate. This reaction requires ATP and arginino-succinate synthetase.
4. *Cleavage of arginino succinate to arginine and fumerate* : The arginino-succinate then splits into arginine and fumarate catayzed by the enzyme arginino succinase.
5. *Cleavage of arginine to ornithine and urea* : This reaction completes the urea cycle and regenerates ornithine. Here hydrolytic cleavage of the guanidine group of arginine is catalyzed by arginase. Ornithine is produced and at the same time urea is formed. This ornithine further couples with carbamyl phosphate.

(Ref. Harper 26th edition)

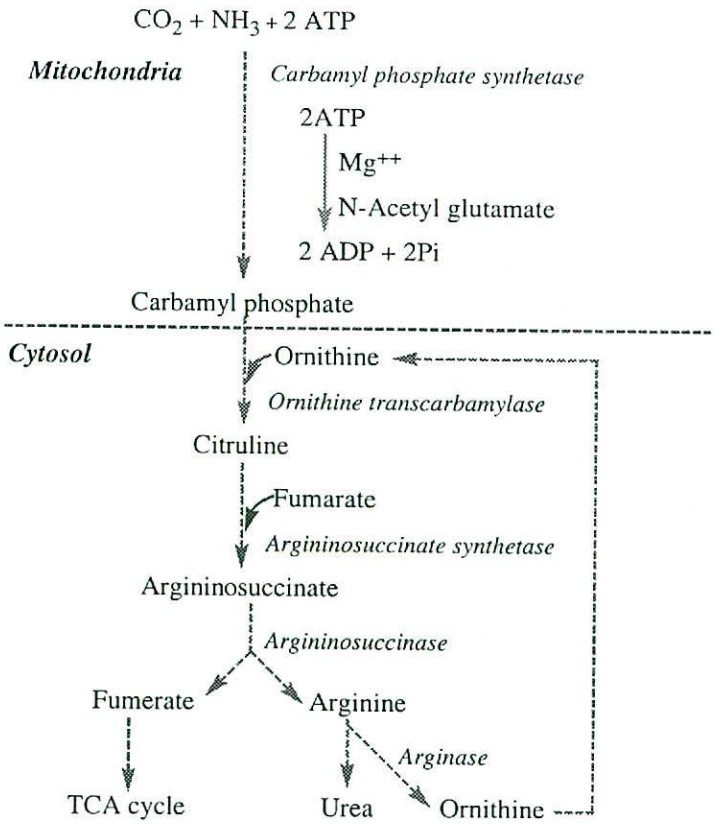


Fig. Diagram of urea synthesis (urea cycle).

Nitrogen balance

Nitrogen balance is the state of the body in which the intake and output of nitrogen are same i.e intake = excretion.

i. *Daily intake of nitrogen* : 16 gm/day
   N_2 content of protein is 16%.
   Normal protein intake/day : 75-100 gm/day
   Intake of nitrogen : about 16 gm/day as protein (16% of protein).

ii. *Daily excretion of nitrogen* : 16 gm/day
   a. Stool and sweat : 2 gm/day
   b. Urine : 14 gm/day
      1. Urea : 85 %
      2. NH_4 : 3 %
      3. Creatinin : 5 % (in fasting increase 15% of total excretion)
      4. Uric acid : 2 %
      5. Undetermined : 5 %

Types of nitrogen balance : It is of two types-

a. *Positive nitrogen balance* : When the intake of protein is more in relation to the nitrogen excretion; then it is called "positive nitrogen balance". i.e growing infant, pregnant mother.
b. *Negative nitrogen balance* : When the excretion of nitrogen is increased than the intake of protein; then it is called negative nitrogen balance i.e kawshiorker, post surgical patient. (-Ve) N_2 balance can be tolerable upto 30%.
c. *Nitrogen equilibrium* : i.e in normal adult.

Importance of nitrogen balance :

1. It reflects the nature of protein utilization in the body and to some extents, an index of physical health.
2. It reflects an index of protein requirement in the body.
3. It measures to some extent of endogenous protein metabolism in the subject.
4. It helps in planning of diet.

Fat metabolism

Blood lipids

i.	Triglycerides	: 35-160	mg%
ii.	Phospholipid	: 145-200	mg%
iii.	Cholesterol	: 150-220	mg%
	a. Cholesterol ester	: 155	mg%
	b. Cholesterol	: 45	mg%
iv.	Free fatty acid (non essential fatty acid)	: 6-16	mg%

Common fatty acids :

1. Saturated fatty acids (50%) : Palmatic acid (16 C), stearic acid (18 C)
2. Unsaturated fatty acids (50%) : Mainly polyunsaturated fatty acid.

Sources of polyunsaturated fatty acids :
i. Fish oil
ii. Vegetable oil except coconut oil, palm oil.

Function : Prevents hypercholesterolaemia.

Plasma level of free fatty acid : 0.1 - 2.0 μeq/ml

Source :

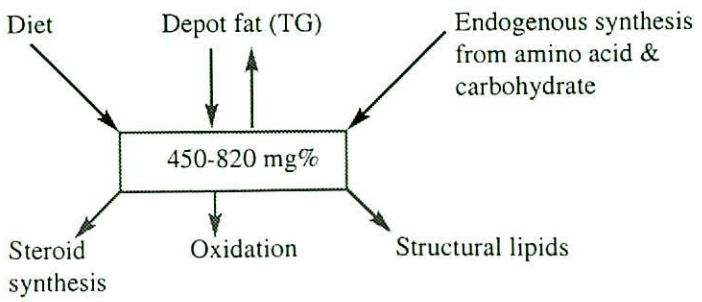
1. Triglycerides of adipose tissue by HSL -ve → In fasting. Well fed → increase insulin → decrease HSL
2. After meal
   i. Chylomicron : By LPL (capillary endothelium of adipose tissue)
   ii. VLDL : By LPL (capillary endothelium of adipose tissue).

   Increase well fed → Increase insulin → Decrease HSL → increase LPL.

Lipid profile

i.	Triglycerides	: < 150	mg%
ii.	Cholesterol	: 150-220	mg%
iii.	HDL	: > 40	mg%
iv.	LDL	: < 130	mg%
v.	LDL : HDL	: 2.5 : 1	
vi.	Cholesterol : HDL	: 3.5 : 1	

Lipid pool : The continuous exchange of blood lipid to the tissue and from tissue to the blood is called lipid pool.



Inflow to blood :

a. Absorped fatty acid & glycerides of the food.
b. By mobilization from depot fat.
c. Synthesis from CHO & proteins.

Out flow from blood :

a. Oxidation in liver
b. Storage in depot fats
c. Formation of structural lipid
d. Formation of milk fat in mammary gland
e. Formation of steroid hormones
f. Formation of lipoprotein complex
g. Formation of ketone bodies.

Factors maintain lipid pool :

1. *Liver* : Liver is predominantly the main organ where synthesis as well as oxidation of lipid goes on side by side.
2. *Endocrine glands* : The anterior pituitary growth hormone and insulin from pancreas greatly affect the lipid pool by affecting metabolism.

Alimentary lipaemia

After a fatty meal, the concentration of plasma lipids begin to rise within 1-2 hours and reaches maximum within 6 hours. This rise of plasma lipids after a fatty meal is termed as alimentary lipaemia.

The chief increase takes place in Neutral fat; phospholipids & cholesterol may also slightly increase.

Sites of fat storage

Large quantities of fat are stored in two major tissues of the body.

i. The adipose tissue
ii. The liver.

Fat depots

Adipose tissue of the body are called fat depots, as they store large quantities of neutral fat.

Depot fat

Definition : The amount of fat that remains stored in the body & is used up during the body need is called depot fat. It constitute about 12% of the total body weight.

Distribution :

i.	Subcutaneous tissue	: 50%
ii.	Perirenal tissue	: 15%
iii.	Mesentry	: 20%
iv.	Omentum	: 10%
v.	Intramuscular connective tissue	: 5%

Composition : Depot fat chiefly composed of the glycerides of various fatty acids and usually Contains 75% of oleic acid, 20% palmitic acid & 5% stearic acid.

Sources :

The depot fat may derived from-

1. Food fat-Chief source
2. Carbohydrate.
3. Proteins.

Functions :

1. Mechanical-
   a. It gives shape to the limbs & body.
   b. It keeps some viscera at position.
   c. Acts as a mechanical buffer aganist injury.
2. Physical : The subcutaneous fat helps in heat regulation.
3. Chemical : It represents stored energy.

Element variable

It represents the fat which disappears during starvation. It is mainly neutral fat.

Element constant

It represents the fat content in the tissue which remains constant even during starvation and can not be reduced without death occuring. It consists mainly of cholesterol and phospholipid.

Antilipotropic factor

Substances which increases the deposition of fat in the liver is called antilipotropic factor.

Example: Cholesterole.

Fate of fat after absorption

After absorption, fat is treated in various ways-

1. It undergoes complete oxidation in the tissues to yeild energy, CO_2 & H_2O. 1 gm of fat oxidized to give 9.3 kcal of heat.
2. Actyl coA an intermediate product, produces aceto acetic acid & contain body component.
3. It is stored in the fat depots (as neutral fat).
4. Fat builds up the structure of many tissues.

(Ref. Wright's)

Metabolic fate of fat

Fats whether derived from food or mobilized from depots, come into the liver. In the liver, with the help of enzyme lipase the fat molecule at first breaks up into fatty acids and glycerol.

Fat $\xrightarrow{Lipase}$ Fatty acid + glycerol.

Fatty acid undrgoes β-oxidation and liberates energy.

Glycerol on oxidation enters into glycolytic pathway as glyceraldehyde.

Difference between element constant & element variable

Element constant (Structural fat)	*Element variable (Depot fat)*
1. It fails to be mobilized during starvation	1. It is mobilized during starvation to meet energy need.
2. It is bound with protoplasm of the cell. So, cannot be extracted with fat solvent.	2. It is present in adipose tissue cells as solvent & can be extracted with fat solvent.
3. It consists mostly of phospholipid & cholesterol.	3. It consists mostly of glycerides, i.e neutral fat.
4. These contain mostly unsaturated fatty acids.	4. These contain mostly saturated fatty acids.
5. It reflects functional activity	5. It is concerned with intermediary metabolism of fat.
6. It can not be shown by histological staining technique.	6. It is possible to show them by staining technique.

Lipotropic factor *(Lipotropins)*

Substances which prevent the deposition of fats and acelerates the rate of removal of fat from the liver, are known as lipotropic factors.

The exact mechanism of action of lipotropic factor is unknown. It is believed that they all help in the synthesis of phospholipid in which form liver fat may be easily mobilized out.

Lipotropic factors are - choline, methionine, betanine, lecithine, inositol, casein & certain other proteins etc.

Beta Oxidation

The process of oxidation of fatty acids is called beta oxidation as the fatty acids are split of successively at betacarbon position i.e. third carbon atom from COOH group. Thus two carbons at a time are removed in the form of acetyl CoA.

Factors of β oxidation :

i. Substrate : Fatty acid
ii. Product : Acetyl CoA
iii. Site : Liver, skeletal muscle, cardiac muscle, adipose tissue
iv. Compartment : Mitochondria
v. No. of acetyl CoA formation from fatty acid :
   Formula : $(^{n}/_{2} - 1)$ number of turns e.g from 16 C palmitic acid → 8 acetyl CoA, by 7 turns.

Stages of beta-Oxidation :

1. *Activation of fatty acid radicle :* In presence of ATP and co-enzyme A, the enzyme thiokinase (Acyl CoA

synthetase) catalyzes the conversion of fatty acid to an active fatty acid or acyl CoA. This is the only step in the complete degradation of fatty acid that requires energy from ATP.

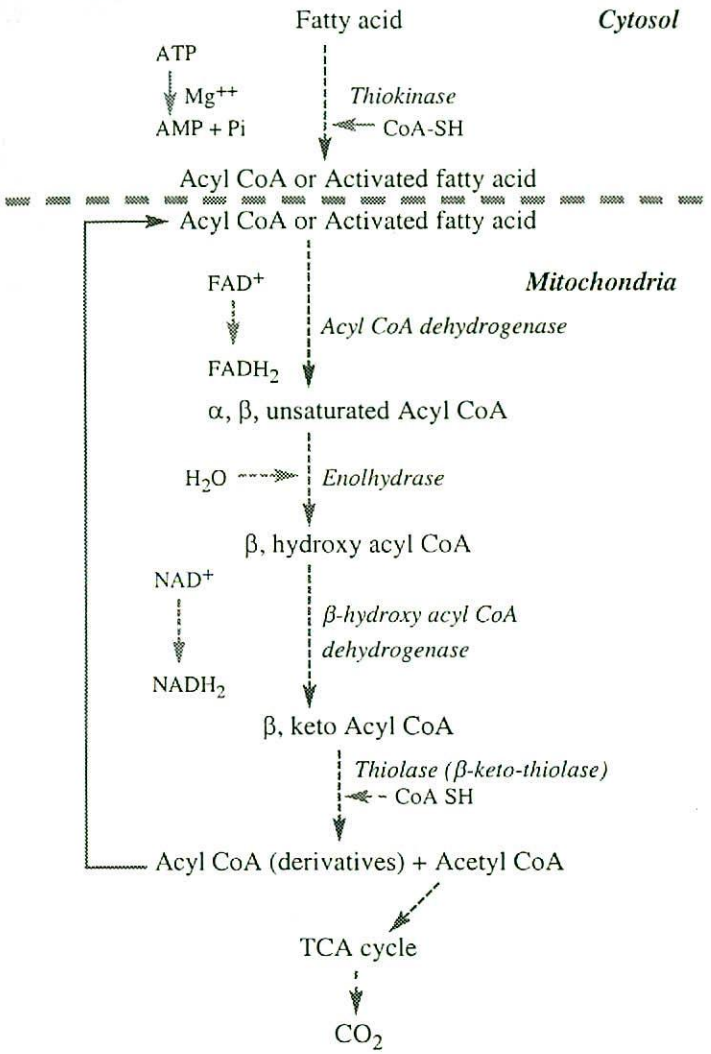


Fig. *Beta-Oxidation of fatty acid.*

2. *Dehydrogenation :* After the formation of acyl CoA, there follows the removal of 2 hydrogen atom from the alpha and beta-carbon (leaving a double bond at this point), catalyzed by acyl CoA dehydrogenase. Thus alpha, beta unsaturated acyl CoA is formed. The co-enzyme for dehydrogenation is flavoprotein.
3. *Hydration :* Then alpha, beta unsaturated fatty acid passes through a process of hydration with the addition of water under the influence of enolhydrase and beta hydroxy acyl CoA is formed.
4. *Dehydrogenation :* There is removal of two hydrogen atoms from beta carbon atoms& beta-keto acyl CoA is produce. NAD acts as a hydrogen acceptor being converted into $NADH_2$. This reaction is catalyzed by beta hydroxy acyl CoA dehydrogenase.
5. *Thiolytic clevage :* Finally beta-keto acyl CoA is split at beta position by thiolase, which catalyzes a thiolytic cleavage involving another molecule of CoA. The product of this reaction are acetyl CoA and an acyl CoA derivative; containing 2 carbons less than the original acyl CoA molecule which underwent oxidation.

   The acyl-CoA formed in the cleavage reaction re-enters the oxidative pathway at reaction number (2) and proceed untill another acetyl-CoA molecule is released. This process is repeated again and again until the entire fatty acid molecule is split into acetyl-CoA. For instance, stearic acid with 18 carbon atoms, nine molecules of acetyl-CoA are formed.

(Ref. Harper 26th edition)

N.B. ***In new born baby*** : Lacking of enzymes of β-oxidation → Gluconeogenesis is imperfect, as gluconeogenesis consumes energy produced in β-oxidation. These babies after long term fasting develop hypoglycaemia → Death (SIDS- sudden infant death syndrome).

Fate of Glycerol

In presence of ATP and glycerol kinase, glycerol is phosphorylated to give glyceraldehyde 3-phosphate (Phospho-glyceraldehyde). This is oxidized to 1-3 diphosphoglycerate which is metabolized by the glycolytic pathway.

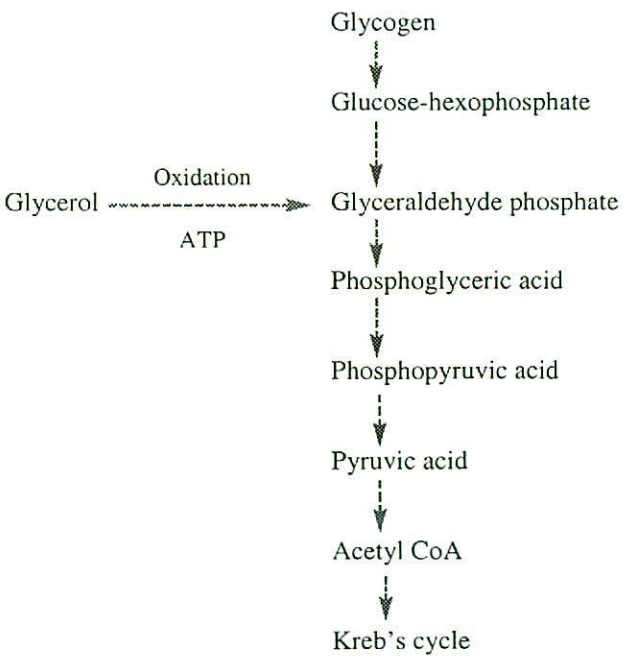


Fig. Metabolic transformation of glycerol.

End product of even number carbon fatty acid

Acetyl CoA :

End products of odd number carbon fatty acid-acetyl CoA & propionyl CoA. Propionyl CoA is formed from three terminal carbon atoms from the methyl end of fatty acids.

Q. ***How many ATP is formed from 1 molecule of stearic acid?***

Ans.

Number of acetyl CoA formation from fatty acid :

Formula : $(^{n}/_{2} - 1)$ number of turns

e.g from 18 C stearic acid 9 acetyl CoA is formed by 8 turns.

One molecule of stearic acid contains 18 carbon atoms. In Beta-Oxidation of stearic acid produces :

i. 9 molecules of acetyl-CoA
ii. 8 molecules of $FADH_2$
iii. 8 molecules of NADH.

So, energy yield :

i. 9 Acetyl CoA	= 12 x 9	= 108	ATP
ii. 8 FAD-2H	= 2 x 8	= 16	ATP
iii. 8 NADH	= 3 x 8	= 24	ATP

Total ATP production = 148 (108 + 16 + 24) ATP.

But in the first reaction 2 ATP is required for the initial activation of fatty acid.

So, net gain of stearic acid oxidation = 146 ATP.

Q. ***How many energy (ATP) is formed from 1 molecule of palmitic acid?***

Ans.

Number of acetyl CoA formation from fatty acid :

Formula : $(^{n}/_{2} - 1)$ number of turns

e.g from 16 C palmitic acid 8 acetyl CoA is formed by 7 turns.

One molecule of palmitic contains 16 carbon atoms. In Beta-Oxidation of palmitic acid produces :

i. 8 molecules of acetyl-CoA
ii. 7 molecules of $FADH_2$
iii. 7 molecules of NADH.

So, energy yield :

i. 8 Acetyl CoA	= 12 x 8	= 96	ATP
ii. 7 FAD-2H	= 2 x 7	= 14	ATP
iii. 7 NADH	= 3 x 7	= 21	ATP

Total ATP production = 131 (96 + 14 + 21) ATP.

But in the first reaction 2 ATP is required for the initial activation of fatty acid.

So, net gain of stearic acid oxidation = 129 (131 - 2) ATP.

Total energy production = 129 x 51.6 = 6656 kilo joul of energy

Phospholipids

Chemistry :Phospholipids belong to the group of conjugated fats,containing sugar alcohol or complex amino alcohol, fatty acid, phosphoric acid & nitrogenous base.

Example : Lecithin, cephalin, sphingomyelin etc.

Blood level : Total phospholipid in blood is 215 mg/100 ml.

Classification : Phospholipid may be classified as-

1. *Monoamino-monophospholipid* : 1 molecule of phosphoric acid, 2 molecule of fatty acids, 1 molecule of glycerol & 1 molecule of nitrogenous base.
   Example : Lecithin, cephalin etc.
2. *Diamino-monophospholipid* : 1 molecule of phosphoric acid and 2 molecule of nitrogenous base.
   Example : Sphingomyelin.

Distribution : The phospholipids are widely distributed in the body and are contained within it. They remain in the cell membrane as well as in the protoplasm. Brain, nervous tissue contain the maximum amount of phospholipids.

Functions :

1. Forms the essential constituent of cell wall.
2. Helps in fat digestion & transport.
3. Protect & maintain the permeability of cell.
4. Helps in tissue oxidation.
5. Helps in blood clotting by depressing the fibrinolytic mechanism.

Cholesterol

1. *Chemistry* : It is a complex monohydric secondary alcohol. With fatty acid it form waxes.
2. *Properties* : It is a stable white crystalline substance, insoluble in water but readily soluble in chloroform, ether, alcohol & other fat solvents.
3. *Blood level* : 150-200 mg/100ml of blood.
4. *Distribution* : It present in all cells-both in the cell membrane & cytoplasm. All body fluids contain cholesterol excepting C SF.

Cholesterol turn over : 1 gm/day

i. *Input* : 1 gm/day
   a. Endogenous production : 500 mg/day
   b. Dietary : 500 mg/day
      Food : Egg, milk, liver, brain, skin etc
ii. *Output* : 1 mg/day
   a. Bile salt : 500 mg/day
   b. Faecal neutral steroid : 400 mg/day
   c. Skin desquamation : 100 mg/day

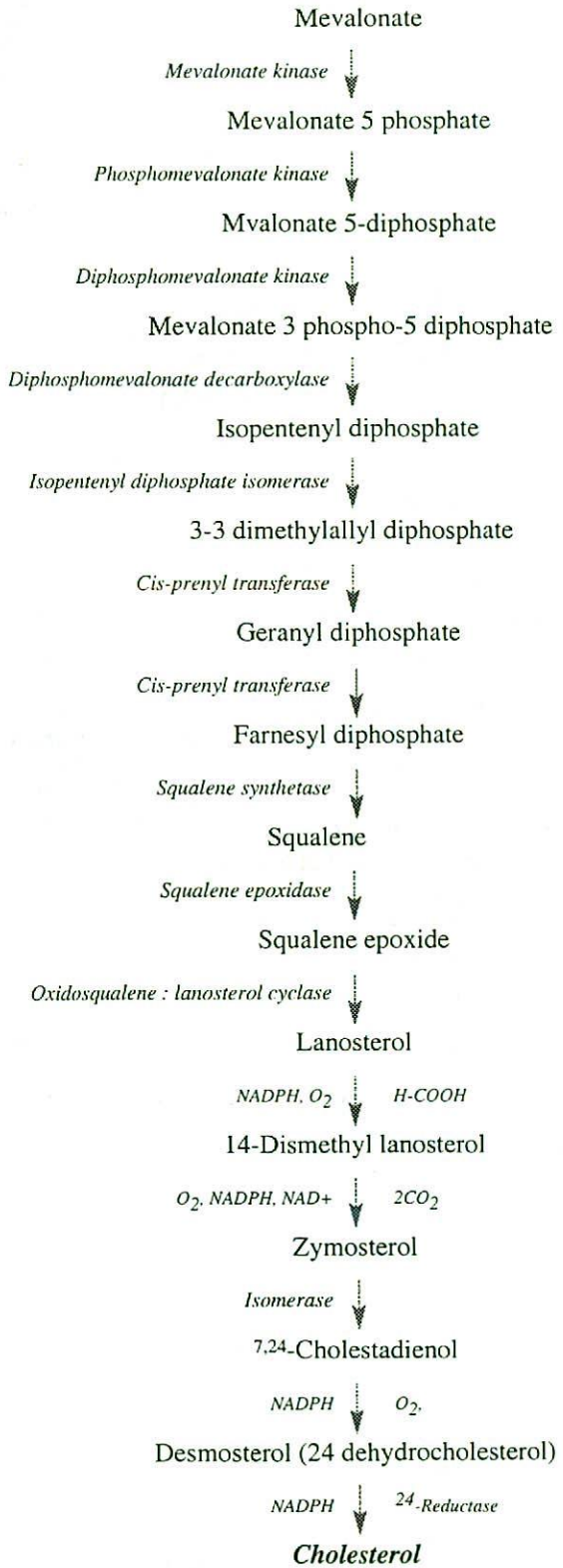
Cholesterol synthesis :

Production site : In steroidogenic organs-

i. Liver
ii. Adrenal cortex
iii. Gonads
iv. Intestine
v. Brain
vi. Skin.

Cholesterol is synthesized in endoplasmic reticulum and cytosol portion of the cell.

Steps of synthesis of cholesterol : The sequence of reactions in the pathway of cholesterol synthesis is given below-

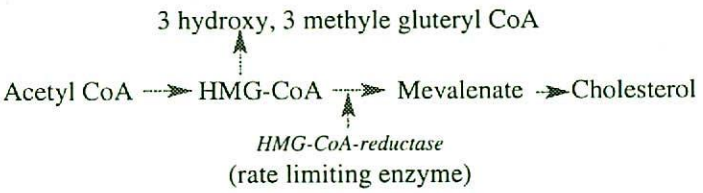


(Ref: Harper's Illustrated Biochemistry 26th Edition, Page-221, 222

1. Activation of acetate to acetyl CoA.
2. Condensation of two acetyl CoA to form acetoacetyl CoA.
3. Formation of 3 hydroxy-3methylglutaryl-CoA (HMG-CoA)
4. Formation of mevalonare.
5. Phosphorylation of mevalonic acid to form 5-phospho mevalonate and 5-diphospho mevalonate
6. The diphosphomevalonic acid after losing CO_2 & H_2O gives rise to form isopentenyl diphosphate.
7. The isopentenyl diphosphate isomerises to form 3-3 dimethylallyl diphosphate which combines with isopentenyl pyrophosphate to give geranyl diphosphate.
8. Another molecule of isopentenyl diphosphate combines with geranyl diphosphate to form farnesyl pyrophosphate.
9. Two molecule of farnesyl pyrophosphate combine to form squalene.
10. An oxidocyclase converts squalene to lanosterol.
11. Lanosterol converts into cholesterol by a number of transformation.

Regulation of cholesterol synthesis :

1. Fasting condition decreases and well fed condition increases cholesterol synthesis.
2. Increase dietary cholesterol decreases cholesterol synthesis and vice versa.
3. Increase insulin and thyroxin decreases cholesterol synthesis.
4. Glucagon and cortisol decreases cholesterol synthesis.
5. Feed back inhibition.



Rate limiting enzyme : Every metabolic pathway is controlled by hormone according to need of the body. This hormones always acts by controlling or stimulating the enzyme in the pathway. This enzyme is called rate limiting enzyme.

* Anti-cholesterol drugs reduce the blood cholestrol by inhibiting rate limiting enzyme HMG-CoA reductase i.e

Increase cholesterol in the cell → Feed back inhibition of HMG-CoA reductase.

Functions of cholesterol :

1. Essential constituent of all cells.
2. Controls cell permeability.
3. Prevents haemolysis.
4. Fat transport.
5. Formation of cholic acid.

6. Antitropic action.
7. Controls cell division.
8. Antagonistic to phospholipids.

Hypercholesterolaemia : Presence of cholesterol in blood above the normal level is called hypercholesterolaemia.

Normal blood level : 150-200 mg/dl of blood.

Relation of cholesterol & atherosclerosis
or coronary heart disease : Cholesterol is the chief pathogenic factor of atherosclerosis. So high cholesterol in food - more chance of atherosclerosis or coronary heart disease.

Chylomicron

Metabolism of chylomicron : By lipoprotein lipase, chylornicrons are metabolized into

i. Chylomicron remnant
ii. Fatty acids: enters into the extrahepatic tissues.
iii. Glycerol
iv. HDL.

Chylomicron remnants are taken up by the liver by receptor-mediated endocytosis. In the liver the cholesterol esters & triglycerides are hydrolyzed into cholesterol & fatty acid.and metabolized.

The LDL (apo B-100, E) receptor and a remnant receptor specific for apo E take part in renmant uptake. Hepatic lipase has a dual role : i. acting as a ligand to the lipoprotein, ii. hydrolizing its TG & phopholipid.

(Ref: Harper's Illustrated Biochemistry 26th Edition)

Keton Body

Keton bodies are :

1. Acetoacetic acid.
2. Beta hydroxy butyric acid.
3. Acetone.

Here acetoacetic acid is called primary keton body.

Normal blood level : 1 mg/100ml of blood.

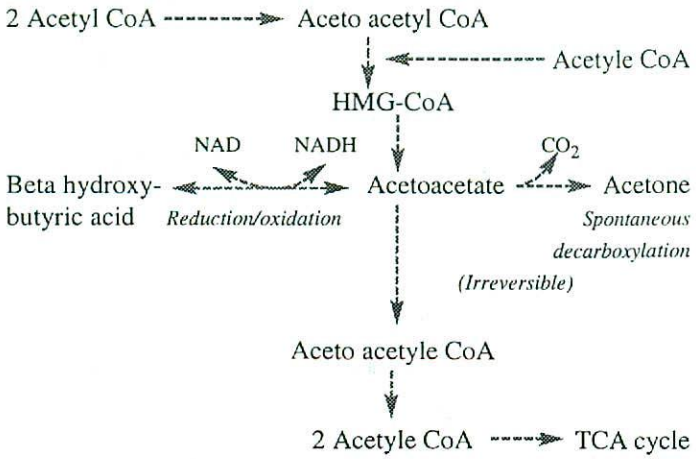
Source of keton bodies : The ketogenic substances are the main source, e.g

i. All the fatty acid.
ii. Ketogenic amino acid, i.e Tyrosine etc.

Site of formation : Liver is the only site.

Mechanism of keton body formation : 2 molecules of acetyl-CoA condense to form acetoacetyl CoA. The reaction is catalyzed by the enzyme beta ketothiolase.
Then by the process of deacylation acetoacetic acid is formed from acetoacetyl CoA. This reaction is catalysed by the enzyme, acetoacetyl CoA deacylase.
When acetoacetic acid is formed, a large portion is converted into beta-hydroxybutyric acid by reduction. This reaction is catalyzed by enzyme beta hydroxybutyrate dehydrogenase.

Small portion of acetoacetic acid is spontaneously converted into acetone by decarboxylation process. It occurs mainly in the lung.



(Ref. Harper 26th edition).

Factors of ketogenesis :

i. Substratre : Acetyle CoA
ii. Product : Ketone body
iii. Site : Only liver
iv. Compartment : Mitochondria

Route of ketone body excretion :

i. Kidney : Beta hydroxybutyric acid, acetoactate
ii. Lungs : Acetone (which is volatile).

Disposal of ketone body :

i. Utilization as metabolic fuel by-
   a. Cardiac muscle
   b. Skeletal muscle
   c. Neurons
ii. Excretion from body.

Most commonly found in blood : Beta hydroxybutyric acid

Ratio : Beta hydroxybutyric acid : Acetone = 3 : 1

Normal ketone body concentration in blood = < 3 mg%
= < 0.2 mmmol/L

Fate of ketone body

I. *Acetoacetic acid* :
   1. It reduces to form beta hydroxy butyric acid.
   2. It decarboxylase to form acetone.
   3. It may reform aceto-acetyl CoA.
   4. It may be used for production of energy.

II. *Beta hydroxybutyric acid* :
   1. It may be converted into acetoacetic acid by reversible reaction.
   2. It is converted into β hydroxy buteryl CoA then aceto-acetyl CoA in the liver.

III. *Acetone :*
1. It may evaporates & passes out through expiration.
2. A small amount is converted into acetoacetic acid.

Acetone :
i. Produced by non enzymatic spontaneous decarboxylation of acetoacetate.
ii. Always excreted through lungs during expiration of air.
iii. Can not be used as metabolic fuel.
iv. Can not cause keto acidosis as it is not an acid.

Antiketogenic substances

These are the substances which prevent the formation of ketone bodies. *They include-*
i. All carbohydrates
ii. Antiketogenic amino acid
ii. Glycerol part of fat.

Some important terms

i. ***Ketonemia*** : Very high concentration of ketone body in blood. Ketonemia is always associated with ketonuria.

ii. ***Ketonuria*** : Increase excretion of ketone body through urine after crossing renal threshold.

iii. ***Ketosis*** : Ketonemia + ketonuria.

Accumulation of abnormal amount of ketone bodies in the tissue and tissue fluids is termed as ketosis, where the urinary excretion of β-hydroxybutyric acid exceeds 200 mg daily (normal 5-10 mg).

Conditions leading to ketosis-
a. Diabetes mellitus.
b. Starvation
c. High fat or low carbohydrate diet.
d. Muscular exercise.

iv. ***Ketoacidosis*** : Ketonemia + ketonuria + ketosis. Acidosis due to keto acids.

Metabolism of ketone bodies :

i. Anabolism : Synthesis of ketone bodies.

ii. Catabolism : After the synthesis in the liver, ketone bodies are transported from the liver and the utilization & oxidation of them occurs in extrahepatic tissues. The main pathway of utilization of ketone bodies in extrahepatic tissues for the activation of acetoacetate to acetoacetyl-CoA involves succinyl-CoA and the enzyme succinyl-CoA-acetoacetate CoA transferase.

Acetoacetate reacts with succinyl CoA, leaving free succinate. Then the acetoacetyl-CoA is splitted to acetyl CoA by thiolase and oxidized in the TCA cycle.

Ketone bodies are oxidized in extrahepatic tissues proportionately to their concentration in the blood.

(Ref Harper's 26th edition)

Biomedical importance of ketone bodies :

1. Ketone bodies are important sources of energy for the peripheral tissues (extrahepatic tissues such as skeletal & cardiac muscle and renal cortex).
2. They are utilized in the brain as fuel during prolonged periods of fasting.
3. In case of starvation & diabetes mellitus, the rate of ketone bodies formation is greater than the rate of their use. So, their concentration begin to rise in the blood (ketonemia) & eventually in the urine (ketonuria).

Ketosis

Definition : Higher than normal quantities of ketone bodies present in the blood or urine constitute ketonemia (hyperketonemia) or ketonuria, respectively. The overall condition is called ketosis.

Causes of ketosis :

I. Physiological cause :
a. Starvation
b. Low carbohydrate diet.
c. High fat diet.

II. Pathological cause :
a. Diabetes mellitus.
b. Pregnancy toxemia.

(Ref Harper's 26th edition)

Production of ketosis in absence of carbohydrate intake :

Absence of carbohydrate intake
↓
Glucose availability in blood becomes less
↓
Liver glycogen is drawn upon in an attempt to maintain the blood glucose
↓
Concentration of insulin in blood decrease & glucagone increase
↓
Glucose utilization in adipose tissue & the inhibitory effect of insulin on lipolysis becomes less
↓
Fat is mobilized as free fatty acids & glycerol
↓
Increase β-oxidation
↓
Increase Acetyl CoA

↓

Increase acetoacetate

↓

Increase Ketone bodies than normal

↓

Ketosis is produced.

Laboratory test of ketone bodies

Normally ketone bodies are absent in urine but in certain conditions (like uncontrolled diabetes mellitus, starvation) are found in urine.

We can detect ketone bodies in laboratory by the Rothera's test.

Method :

i. 3 ml of urine is saturated with $(NH_4)_2SO_4$ taken in a test tube

ii. Add few drops of 5% Na-nitroprusside & shake

iii. Add cone. NH4OH solution by the side of test tube

iv. Purple coloured ring develops at the junction of two liquids

Result : Presence of Ketone bodies in urine.

Ketoacidosis

i. *Definition* : Ketone bodies are acidic and when produced in excess over long periods, causes a condition known as ketoacidosis (as in diabetes mellitus).

ii. *Mechanism of formation of ketoacidosis in diabetes meliitus* : Decrease insulin causes increase lipolysis to liberate fatty acids. Liver uptakes this fatty acids & converted it into acetyl-CoA. Normally acetyl-CoA enters the TCA cycle but in absence of insulin, more acetyl-CoA is formed than can enter the cycle. This excess acetyle-CoA is converted to acetoacetic acid which, later on, converted to other ketone bodies and forms ketoacidosis.

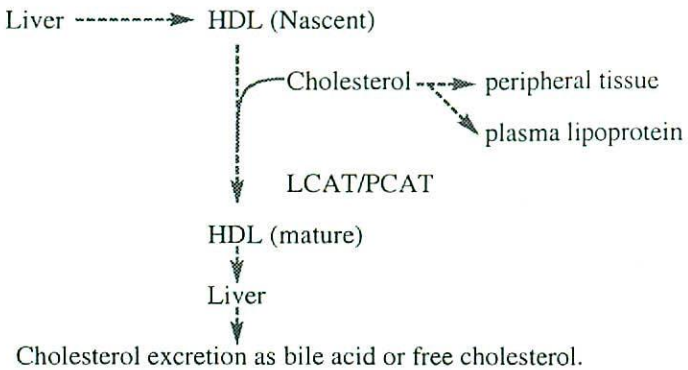
i.e Lack of insulin → Increase catabolism → Increase glycogenolysis, increase gluconeogenesis, increase lipolysis → Increase FFA in plasma → Increase β-oxidation → Increase Acetyl-CoA → Increase Acetoacetate → Increase Ketone bodies → Hyperketonemia → Acidosis → *Diabetic ketoacidosis.*

Physiological basis of treatment of keto acidosis :

Physiological basis of treatment of keto acidosis is to achieve as possible as normal metabolism. Ketoacidosis can be treated by giving-

1. Appropriate insulin
2. Oral hypoglycaemic agents
3. Diet containing
   i. Protein : Anti-ketogenic amino acids (e.g glycine, alanine etc.)
   ii. All carbohydrate
   iii. Fat : Glycerol part.

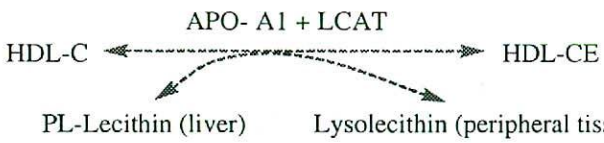
HDL metabolism (scavenger of periferal tissue)



Function of HDL :

i. Pick up cholesterol from peripheral tissue, backs to the liver and facilitate excretion.

ii. *Reverse cholesterol transport* :



Cholesterol after coming incontact with HDL, converted to cholesterol ester and captured by addition of fatty acid phospholipid; converted to lysolecithin.

In liver : Reverse reaction occurs and cholesterol become free from HDL. This is called *reverse transport of cholesterol.*

Importance : Maintenance of normal cholesterol level static.

SDA

The specific dynamic action (SDA) of a food stuff is the extra heat production over and above the caloric value of a given amount of food, which is produced when the food is used by the body.

Specific dynamic action of :

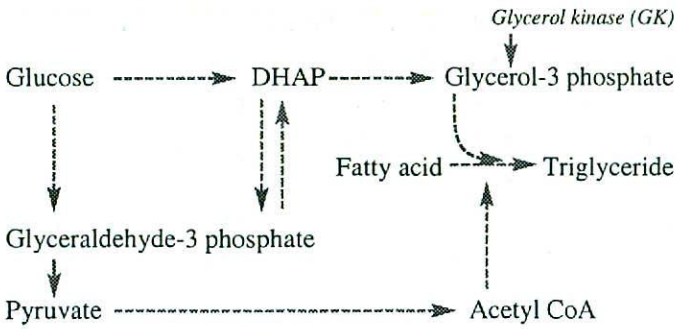
i. Protein : 30%

ii. Fat : 23%

ii. Carbohydrate : 6%

Synthesis of triglyceride (TG) from Glucose :

CHO (carbohydrate) very quickly convert to fat.



Glycerokinase enzyme present only in liver. So fat synthesis occur in liver & adipose tissue. In case of adipose tissue there is no glycerokinase. So fat synthesis occur through formation of pyruvate via EM-pathway. So continuous supply of glucose should ensured i.e dependent on insulin.

Role of insulin :

A. Decrease glucose entry to adipocyte
B. Increase hormone sensitive lipase
↓
Increase breakdown of triglyceride
↓
Increase fatty acid in the liver
↓
Increase fatty acid in the blood.

Hormones of integrated metablism :

i. Insulin
ii. Glucagon
iii. Catecholamines
iv. Cortisol
vi. Growth hormones.

Fuel reserve :

i. Triglycerides : 80 % (1-1.5 lac K.cal)
ii. Glycogen : (1100 K.cal)
iii. Protein : 35000 K.cal).

Fuel interconversion :

Carbohydrate ----------→ Fat
Carbohydrate ←----------→ GAA
Amino acid ----------→ FAT.

Fuel profile :

	Fed *0-4 hours*	*Fasting* *4-24 hours*	*Short starvation* *1-7 days*	*Long starvation* *>7 days*
i. Brain	Glucose	Glucose	Glucose	ketone body
ii. Heart	Fatty acid	Fatty acid	Fatty acid ketone body	Ketone body Fatty acid
iii. Skeletal muscle	Glucose	Fatty acid	Fatty acid Ketone body	Fatty acid

Brain intake

i. Fasting to short starvation : Glucose intake from-
   a. Glycogenolysis
   b. Neoglucogenesis
ii. Long starvation : Ketone body.

Metabolism in well fed condition (2-4 hours after meal)

i. Increase glycogenesis
ii. Increase lipogenesis
iii. Increase protein synthesis
iv. Increase HMP-shunt
v. Increase glycolysis in brain and skeletal muscle.

Metabolism in starvation

Aims :

i. Maximum use of triglycerides
ii. Maintenance of blood glucose concentration
iii. Increase ketone body synthesis
iv. Decrease body catabolism.

In fasting (4-24 hours after meal)

i. ↑↑↑ Glycogenolysis
ii. Lipolysis
iii. Gluconeogenesis
iv. Ketogenesis.

In short starvation (24 hours to 7 days)

i. ↑↑↑ Gluconeogenesis
ii. ↑↑↑ Proteolysis
iii. ↑↑↑ Lipolysis
iv. ↑↑↑ Ketogenesis.

In prolong starvation (>7 days)

i. ↓↓ Gluconeogenesis and proteolysis
ii. ↑↑↑↑ Lipolysis and ketogenesis further increase.

Diabetes

Metabolic changes in type I diabetes

Hyperglycemia and ketoacidasis are the hallmarks of untreated diabetes mellitus.

i. *Hyperglycemia* is caused by increased hepatic production of glucose combined with diminished peripheral utilization.
ii. *Ketosis* results from increased mobilization of fatty acids from adipose tissue combined with accelerated hepatic synthesis of 3-hydroxybutyrate and acetoacetate.
iii. However, not all the fatty acids flooding the liver can be disposed of through oxidation or ketone body synthesis. Fatty acids are also converted to *triacylglycerol*, which is packaged and secreted in *VLDL*.
iv. Chylomicrons are synthesized from dietary lipids by the intestinal mucosal cells following a meal. Because lipoprotein degradation catalyzed by *lipoprotein lipase* in adipose tissue is low in diabetics, the plasma chylomicron and VLDL levels are elevated, resuting in ***hypertiglyceridemia***.

v. These metabolic changes result from a deficiency of *insulin* and a relative excess of *glucagon*, the latter playing a critical role in stimulating *gluconeogenesis* and *ketogenesis*.

(Ref. Lippincott's Illustrated Reviews of Biochemistry, 3rd Edition)

Chronic effects of diabetes

The long-standing elevation of blood glucose is widely believed (but not conclusively proved) to cause the *chronic complications of diabetes-*

i. Premature atherosclerosis
ii. Retinopathy
iii. Nephropathy
iv. Neuropathy.

Intensive treatment with insulin delays the onset and slows the progression of these long-term complications. The benefits of tight control of blood glucose outweigh the increased risk of severe hypoglycemia. How hyperglycemia causes the chonic complications of diabetes is unclear. In cells where entry of glucose is not dependent on insulin, elevated blood glucose leads to increased intracellular glucose and its metabolites. For example, increased intracellular sorbitol may contribute to the formation of cataracts. Further hyperglycemia may promote the condensation of *glucose* (or *its metabolites*, particularly *Glyceraldehyde 3 phoshate*) with cellular *proteins*, in a reaction analogous to the formation of HbA_{1c}. These glycated proteins may mediate some of the early microvascular changes of diabetes.

(Please see page 130 of Lippincott's Illustrated Reviews of Biochemistry for discussion of the sorbitol pathway).

(Ref. Lippincott's Illustrated Reviews of Biochemistry, 3rd Edition)

Comparison of two types of diabetes mellitus

	Insulin-dependent diabetes mellitus (IDDM)	*Non-insulin-dependent diabetes meliitus (NIDDM)*
Synonym	Type I; juvenile-onset diabetes	Type II : adult-onset diabetes
Age of onset	Usually during childhood or puberty	Frequently after age 35
Nutritional status at time of onset of disease	Frequentlv undernourished	Obesity usually present
Prevalence	10%-20% of diagnosed diabetics	80%-90% of diagnosed diabetics
Genetic predisposition	Moderate	Vety strong
Defect or deficiency	β-Cells destroyed, eliminating production of insulin	Inability of β-cells to produce appropriate quantities of insulin : *insulin resistance*
Ketosis	Common	Rare
Plasma insulin	Low to absent	Normal to high
Acute complications	Ketoacidosis	Hyperosmolar coma
Oral hypoglycemic drugs	Unresponsive	Responsive
Treatment with insulin	Always necessary	Usually not required.

Temperature

Heat

The thermal condition of the body is called heat.

Temperature

The degree of hotness and coldness of the body is called temperature.

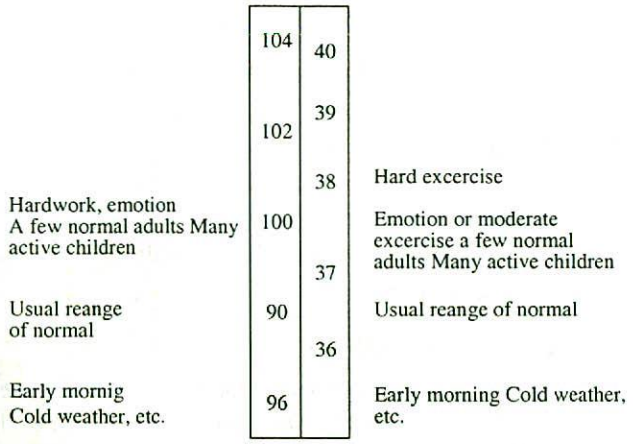
Normal body temperature

Range : 97-99 °F or
: 36. 0-37.5 °C

Average : 98.6 °F or 37 °C

1. Oral temp : 98.0 °F - 98.6 °F (36.7-37 °C)
2. Rectal : (98.0 + 1) °F = 99.0 °F
3. Axillary : (98.0-1) °F = 97.0 °F

(Ref. Guyton & Hall 11th edition)



Estimated range of body temperature in the normal persons (From Dubois Fever Springfield, iii., Charles C Thomas

Fig. 15-1. *Estimated range of body temperature.*

Core temperature : The temperature of the interior of the body is called core temperature.

Shell Temperature : The temperature of the skin or tissues immediately undrlying the skin is called shell temperature.

Difference between core and shell temperature

Core temperature	*Shell temperature*
1. Core temperature remains almost exactly constant. It varies within ±1°F.	1. Shell temperature rises and falls with the temperature of the surroundings.
2. It is determined by measuring i. Rectl and	2. It is determined by measuring i. Oral and
ii. Esophageal temperature.	ii. axillary or groin temperature.
3. Genereally temperture is more than shell temperature.	3. Generally the temperature is less than core temperature.

Q. **How the heat is conducted from the core of the body to the skin?**

Ans. Blood vessels penetrate the subcutaneous insulator tissues and are distributed profusely in the subpapillary portions of the skin. Indeed immediately beneth the skin is a continuous venous plexus that is supplied by inflow of blood. In the most exposed areas of the body- the hands, fet and ears blood is supplied through direct arterivenous anastomoses, from the arterioles to the veins. Therefore the flow of blood to the skin is the most of effective mechanism of heat transfer from the body core to the skin.

(Ref. Guyton & Hall 11th edition)

Thermal balance

It is the state of condition when the rate of heat production is exactly equal to the rate of heat loss. The thermal balance is maintained by thermogenesis and thermolysis.

Thermogenesis : It is the process of heat production of the body.

Mechanism of heat gain

We gain heat by two ways :

A. ***Heat production within the body*** : It occurs in the follwing ways :

1. *Metabolism :* Oxidation of food meterials produces large amount of heat in the body.
2. *Physical activity :* The skeletal muscles produce about 1/2 of the body heat during exercise, walking, running and other form of physical activity.
3. *Metabolic activity* of liver, heart etc. produce heat.
4. *Action of some hormones :* Such as thyroxine, epinephrine and enzyme also produce heat.
5. *Peristaltic activity* of intestine during digestion also produce heat.

B. ***Heat gain from environment*** :

1. By directly from sun and heated substance.
2. Ingestion of hot foods and drinks.

Thermolysis : It is the process of heat loss from the body.

Mechanism of heat loss from the body

Heat is lost from the body by :

1. *Radiation :* Transfer of heat from one object to another without the contact with each other. Heat is transfered by radiation in the form of electro- magnetic waves. Due to the difference of temperature existing between body and envirment about 60% of total body heat is lost by radiation.
2. *Conduction :* Transfer of heat from atom to atom or molecule to molecule by change of Kinetic energy (KE). When the temperature of the air is low, about 18% of heat is lost in this process, 15% of the heat is conducted to the air and 3% is lost by direct conduction from the surface of the body to other objects.

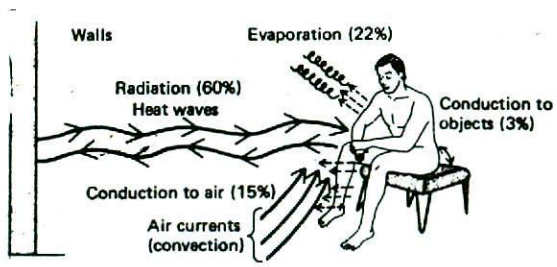


Fig. 15 - 2. *Mechanism of heat loss from the body.*

3. *Convection :* Transfer of heat by movement of molecule of a fluid or gass. When the temperature of the surrounding air is low, heat is lost by the skin and the molecules of air gradually get warmed and move away from the surface. A new layer of cooling air takes its place and the process is continue.
4. *Evaporation :* Heat loss occurs due to evaporation of sweat. About 22% heat is lost in this way through lung and skin. *It has two types :*
   a. Insensible perspiration
   b. Sweating.

   Water evaporates insensibly from the skin and lungs, this causes continual heat loss from the body (12 to 16 cals per hour). When the temperature of the surroundings is greater than that of the skin, instead of losing heat, the body gains heat by radiation and conduction. Under this condition, the only means by which the body can rid itself of heat is by evaporation.
5. *Heat is lost through feces and flatus.*
6. *Heat is lost through urine.*

(Ref. Guyton & Hall 11th edition)

Factors influencing body temperature

A. ***Physiological*** :

1. *Age :* Body temprature is more in growing children but it is lower in old age.
2. *Sex :* It is more in male than female.
3. *Diurnal changes :* It is highest in the evening (4 to 6 P.M.) and lowest at the morning (3 to 5 A.M.)
4. *Diet :* Protein diet rises the temperature more compared to fat and carbohydrate. It is menifested during the process of digestion.
5. *Muscular activiy :* It rises body temperature.
6. *Climatic variation :* Temperature changes with climatic variation.
7. *Menstruation :* During menstruation temperature falls, but during ovulation temp. rises.
8. *Sleep :* Temperature fall during sleep.
9. *BMR :* Change of BMR affect the temperature.
10. *Emotion :* Rises body temperature.
11. *Miscellaneous :* Clothing, air movement, humidity etc influence the body temperature.

B. ***Pathological*** :

1. Administration of pyrogens : It rises body temperature.
2. Endocrine disordrs :

   In *thyrotoxicosis* body temperature rises.

   In *myxoedema & cretinism* temperature fall. *Diabetes insipidus and pontine haemorrhage* rises the temperature, whereas *Diabetic coma, Hypopituitarism* and *Hypotha- lamic lesion* lowers the temperature.

Hypothalamic thermostate

The overall heat controlling mechanism of the hypothalamus is called the hypothalamic thermostate.

Temperature regulating centers :

There are two temperature regulating centers, located in the hypothalamus :

a. Anti-rise center, located in the anterior part of hypothalamus.
b. Anti-drop center, located in the posterior part of hypothalamus.

(Ref. Guyton & Hall 11th edition)

Regulation of body temperature

Body temperature is regulated by :

1. Hypothalamic thermostate.
2. Behavioral control.
3. Local skin reflex.

Hypothalamic thermostate : The temperature of the body is regulated almost entirely by nervous machanism of hypothalamic thermostate and almost all of these operate through temperature regulation centers by increasing or decreasing body temperature.

a. *Mechanism of Reducing body temperature :* When the temperature becomes too great, thermostatic system employs three important mechanism to reduce body temperature.
   i. Skin blood vessels of almost of all areas of the body dilated.
   ii. Sweating is strongly stimulated.
   iii. Shivering and chemical thermogenesis are strongly inhibited.

b. *Mechanism of increasing body temperature :*
   In cold state, the thermostatic mechanism increasing body temperature by :
   i. Skin vasoconstriction throughout the body.
   ii. Pilo-erection (Not important for human being)
   iii. Increase in heat production by :
      a. Shivering
      b. Sympathetic excitation of heat production.
      c. Thyroxine secretion.

(Ref. Guyton & Hall 11th edition)

Behabioral control : The obvious types of behavioral adjustment include-

i. Selecting approprite clothing
ii. Moving the body to a different environment setting
iii. Increasing in the delivery of heat or cold from appropriate heaters or air conditionar and so forth.

(Ref. Guyton & Hall 11th edition)

Local skin reflex : When a person places a foot under a hot lamp and leaves it there for a short time, local vasodilation and mild local sweating occur. Conversely, placing the foot in cold water causes vasoconstriction and cessation of sweating. These reaction are caused both by local effect of temperature change directly on the blood vessels and sweat glands.

(Ref. Guyton & Hall 11th edition)

Maintenance of body temperature in cold weather

When a person is exposed to extreme cold, the cold receptors of skin send sensory signal to the cold sensitive area of hypothalamus which then stimulate the temperature increasing mechanism of the body. *These are-*

1. ***Skin vasoconstriction throughout the body*** : Stimulation of the hypothalamic sympathetic center casuses vasoconstriction of the peripheral blood vessels reduced blood flow to the skin there by decreasing heat loss and increases body temperature.
2. ***Increase in het production by shivering*** : Cold signal excited the center for shivering of posterior hypothalamus, which then discharge rhythmic signals to skeleton muscle and increase the muscle tone throughout the body and shivering begins- causes heat production.
3. ***Sympathetic excitation of heat production*** : Sympathetic excitation increases the rate of metabolism thereby increasing the body temperature.
4. ***Thyroxin secretion*** : Celling of hypothalamus increases the release of thyrotropin releasing hormone from hypothalamus which then acts on anterior petuitary causes secretion of TSH. This then stimulate the thyroid gland to secrete thyroxin. This thyroxin increases the rate of cellular metabolism thereby increasing body temperature.

   In this way body maintains its normal temperature during cold season.

(Ref. Guyton & Hall 11th edition)

Mechanism of maintaining temperature in hot weather

In hot weather the body temperature become too great. The thermostatic system then employs three important mechanism to reduce body heat. *These are :*

1. *Vasodilatation* : In hot weather the skin blood vessel are intensly dilated due to inhibition of sympathetic centers in the posterior hypothalamus that cause vasoconstriction. This increases the blood flow to the skin and also increases heat loss thereby decreasing the body heat.
2. *Sweating* : Stimulation of the preoptic area in the anterior hypothalamus cause transmission of impulse through the autonomic pathway to the spinal cord and thence through sympathetic nerve fibre to the sweat gland which then increases sweating and the body heat lost along with sweat by the process of evaporation.
3. *Decrease in heat production* : Those mechamism that cause excess heat production such as shivering, chemical thermogenesis are strongly inhibited and decreases the body heat production.

   In this way, body maintain its normal temperature in hot climate. *(Ref. Guyton & Hall 11th edition)*

Q. **Why shivering follows on exposure to intense cold?**

Ans. When a person exposed to extreme cold, (temperature below 25°C) causes stimulation of cold receptors (Krause's end bulb). The impulse passes from the krause's end bulb to the centre of shivering. It sends afferent impulses to the anterior horn cells via lateral column of spinal cord. This impulse increases the tone of skeletal muscles through out the body and there occurs reflex twitches (uncordinated) at first of the muscles of the body which increase in intensity. Ultimately leading to rhythmic slow contraction and menifest shivering.

Hormonal control of temperature

i. *Catecholamine* : It causes increase metabolism and vasoconstriction.

Effects : Increase heat production.

ii. *Thyroid hormone* : It causes increase metabolism; synergistic action with catecholmines

Effects : Increase heat production.

iii. *Cortisol* : It potentiate the catecholamine.

Effects : Antidrop response.

iv. *Thyroid stimulating hormonr-TSH* and *ACTH* : TSH causes thyroid hormone secretion and ACTH causes cortisole secretion.

Effects : Antidrop response.

Thermal counter-current system

In excessive cold condition cutaneous vessels become more sensitive to catecholamines and so, arterioles and venules are constrict. This causes flow of blood from artery to deep vein without reaching the skin and carried back into the heart. This is called thermal counter current system.

Fever

a. *Definition* : An elevation of the normal body temperature is called fever.

b. ***Pathogenesis*** :

Endotoxin, inflammation and other pyrogenic stimuli
↓
Stimulate monocyte, macrophages and kuffer cells
↓
Produce interleukin-1
↓
Acts on preoptic area of hypothalamus
↓
Prostaglandin
↓
Fever.

or Inflammation → Prostaglandin → Fever.

c. ***Benefit of fever*** :

1. Inhibit growth of microorganisms
2. Increase antibody production
3. Inhibit tumor growth.

However, a very high temperature is harmful

d. ***Classification of fever*** :

i. *Continued fever* : When fever does not fluctuate more than 1°C during 24 hours and at no time touches the normal called continued fever.

ii. *Remittent fever* : A fever, which fluctuates (daily 2°C) but does not return to normal temperature is called remittent fever.

iii. *Intermittent fever* : Fever only for several hours during the day is called intermittent fever.

iv. *Relapsing fever* : Periods of fever interspersed with periods of normal temperature is called relapsing fever.

(Ref. Guyton & Hall 1th edition & others)

Hyper-pyrexia : When the body temperature rises above 41.2°C or 106°F it is called hyperpyrexia. This is accompanied by increased heart rate, respiratory rate, great discomfort, weakness, prostration, headache, mental confusion and ultimately loss of consciousness occurs.

Rise of temperature above 43°C or 109°F and its persistence for a certain length of time results in death.

Sweating

1. *Sweat* : Sweat is the secretion from sweat glands.
2. *Sweating* : The process of secretion of sweat from the sweat gland is called sweating. Skin temperature at which sweating begins is about 34°C.
3. *Mental sweating* : Sweating which occurs due to emotion, anxiety is called mental sweating. It occurs in the palm of hand, sole of foot, forehead, neck etc.
4. *Thermal sweating* : Sweating which occurs due to rise of external or body temperature is the called thermal sweating. It is controlled by hypothalamus.

Function of sweating :

i. It is concern with the regulation of temperature
ii. It is concern with the maintenance of water, electrolytes and acid-base balance.
iii. It performs some excretory function
iv. It keeps the skin moist.

Q. **Why during evaporation body heat is lost?**

Ans. When water evaporates from the body surface; 0.58 calorie (kilocalorie) of heat is lost for each gram of water that evaporate. Even when a person is not sweating, water still

evaporate insensibly from the skin and lungs at a rate of about 600 milliliter per days. This cause continual heat loss at a rate of 12 to 16 calorie per hour. This is the way of heat loss during evaporation.

(Ref. Guyton & Hall 11th edition)

Chills

i. *Definition* : An attacked of shivering accompanied by the sensation of coldness even the body temperature (set point 100°F) is above normal is called chills.

In this condition normal set point changed higher than nor value.

ii. *Effects* :
   a. Piloerection
   b. Vasoconstriction
   c. Epinephrine secretion
   d. Shivering.

Heat stroke

i. *Definition* : A condition or derangement of the heat control centers due to exposure to very high temperature is called heat stroke.

Heat stroke is an acute life-threatening situation when body temperature is above 41°C.

ii. *Condition for heat stroke* : In hot, humid climates with little cooling wind, even without exercise.

iii. Body temperature (>41°C or 106°-108°F) → Hypothalamic heat regulating ability depressed → Sweating diminished. This condition is called heat stroke.

iv. *Symptoms and signs* :
   a. The patients suffer from headache, nausea, vomiting, and weakness.
   b. The skin is hot.
   c. Sweating is often absent.
   d. Neurological involvement leads to confusion, delirium eventually coma.

v. *Complications* :
   a. Dry burning skin (the hot dry man)
   b. Loss of conciousness
   c. Cerebral edema
   d. Renal and hepatic failure.

Heat exhaustion

i. *Definition* : This usually occurs in subjects who are not acclimatized and who undertake heavy exercise.

ii. *Cause* :
   a. Water depletion : Water loss can be as high as 5-6 liters per day.
   b. Salt and water depletion, due to sweating : Salt loss may be up to 20 gm.

iii. *Symptoms* :
   a. Giddiness
   b. Generalized fatigue
   c. Weakness
   d. Dehydration and delirium
   e. Syncope.

Heat cramps

i. *Definition* : These are painful cramps in the muscles (usually of the legs) after exercise.

ii. *Cause* : They often occur in fit young people when they take vigorous exercise in hot weather.

iii. *Symptoms* : Symptoms are thought to be the result of low extracellular sodium caused by replenishment of water but not salt during prolonged sweating.

Hypothermia

i. *Definition* : Decrease body temperature below normal (below 34°C) is called hypothermia.

Mild hypothermia (32-35°C) causes shivering and initially a feeling of intense cold.

Severe hypothermia occurs when core temperature becomes below 32°C.

Following emersion in cold water dangerous hypothermia can develop after several hours (immersion at temperature of 15-20°C). Below 12°C the patient's limbs become anaesthetized and paralyzed and take some hours to recover after the patient is rescued.

ii. *Causes* :
   1. Accidentally occurs in babies
   2. Exposed to low temperatures
   3. Associated with certain diseases :
      Addison's disease
      Myxoedema
      Cerebrovascular accident
      Uraemia
      Muscular paralysis.

iii. *Symptoms and signs* :
   a. Patient becomes cold and pale
   b. Pulse rate and volume fall
   c. Systemic blood pressure falls
   d. Stiffness of muscle
   e. Unconsciousness (below 27°C)
   f. Tendon reflexes are depressed
   g. Pupillary and other brain-stem reflexes are lost
   h. Death follows usually from ventricular fibrilations.

Frostbite

i. *Definition* : The formation of the ice crystals in the skin and superficial tissues begins when the temperature falls to -3°C; ambient temperatures generally have to be below -6°C for this to occur.

ii. *Characteristics* :
   a. *Frostbitten tissue* : is pale, grayish and initially doughy to the touch. Later it freezes hard, when it looks (and feels) like meat taken from a deep freeze.
   b. *Hands* and *feet* : that have lost their feeling are an important feature when the temperature is below -5°C, as frostbite may then develop insidiously.

Q. 01. **Which part of the temperature is more accurate?**

Ans. Core temperature is more accurate i.e rectal temperature.

Q. 02. **Why a person feels cold in a fever of rapid onset?**

Ans. The set point of the hypothalamus integrating center has risen to a high level, so the subject feels cold until his core temperature is raised to match the new set point.

Q. 00. **Describe the innervation of sweat gland.**

Ans. Sympathetic cholinergic fibres innervate sweat gland.

Q. 00. **What hormonal changes occurs in cold environment.**

Ans. In cold environment secretion of catecholamnines and thyroid hormones secretion is increased.

Q. 00. **What is insensible heat loss?**

Ans. Loss of heat through respiratory system and skin is called insensible heat loss. Insensible loss occurs in all weather in any condition. 20-25% basal heat production loss in this way.

Q. 00. **What is set point?**

Ans. It is a level of the critical body core temperature (exactly 37.1°C) that is always maintained by the temperature control mechanisms in any condition (excess heat or cold).

15.7

Temperature

Q. 01. **For each 1o F rise of temperature, cerebral blood flow falls by**

T a. 4%
F b. 1%
F c. 2%
F d. 7%
F e. 3%.

Q. 02. **False about body temperature**

T a. AM temperature > 98.4° F
F b. Mean temperature 98.2° (+/-) 0.7° F
F c. PM temperature > 99.9° F
F d. Rectal temperature 0.6° F > oral temp.

Q. 03. **Physiologic changes in heat acclimatization are :**

T a. increased aldosterone secretion
T b. decreased loss of salt in sweat
T c. increased sweating
F d. decreased plasma volume
F e. increased loss of salt in urine.

Q. 04. **Normal body temperature is**

T a. is increased during exercise
T b. about 98.6°C
T c. determined by the balance between heat production and loss
T d. lowest during sleep
F e. elevated in hypothyroidism.

Q. 05. **Body heat is produced by**

T a. hunger
T b. muscular activity
F c. respiration
F d. urination
F e. defecation.

Q. 06. **Body heat is lost by**

T a. anorexia
T b. increased respiration
T c. radiation
F d. horripilation
F e. hunger.

Q. 07. **Temperature regulating mechanism activated by cold are**

T a. increased secretion of epinephrine
T b. shivering
T c. curling up
F d. cutaneous vasodilatation
F e. apathy and inertia.

Q. 08. **Temperature regulating mechanism is activated by warm are**

T a. anorexia
T b. increased respiration
T c. sweating
F d. shivering
F e. increased muscular activity.

Q. 09. **Heat is produced by**

T a. epinephrine
T b. shivering
T c. thyroxine
F d. decreased metabolism
F e. insulin.

Q. 10. **Response in hot environment are**

T a. vasodilation
T b. sweating.
T c. increased heat loss
T d. decreased heat production
F e. vasoconstriction.

Q. 11. **Response in cold environment are**

T a. vasoconstriction
T b. pilo-erection.
T c. decreased heat loss
T d. increaser heat production
F e. vasodilatation.

Q. 12. **When a healthy individual is exposed to cold, following changes occurs :**

T a. increased catecholainines secretion
T b. surface temperature is decreases more than core temperature
F c. total peripheral vascular resistance decreases
F d. adjustments are controlled from centers in the medulla
F e. shivering decreases the body temperature

Q. 13. **When a normal individual is exposed to a hot environment following changes occurs**

T a. Excessive sweating
T b. Increased resting cardiac output

T c. Decrease urine volume
T d. Cutaneous vasodilatation
F e. Reflex increase in ventilation is the major way of increase heat loss.

Q. 14. **The core temperature of an individual is above normal**
T a. As a result of administration of progesterone
T b. As a result of administration of adrenaline
T c. Exercising strenuously
T d. As a result of administration of pyrogens
F e. With deficiency of thyroid function.

Q. 15. **When a normal adult human from a temperate climate adapts to a tropical climate, there is a decrease in**
a. thyroxine producion
b. the vascular peripheral resistance
c. the salt concentiation of sweat
d. the overall rate of heat loss from the body
e. The basal metabolic rate.

Q. 16. **In hypothermia**
T c. Tendon reflexes are depressed
T e. Death occur due to ventricular fibrillation
F d. Muscle become flaccid
F a. Temperature usually falls below 25°C
F b. Pulse become rapid.

Q. 17. **Following hormones are involved in temperature regulation :**
T a. Thyroxine
T b. Norepinephrine
F c. Aldosterone
F d. Somatostatin
F e. Substance-P.

Q. 18. **Regarding shivering**
T a. It is mediated by somatic nerve
T b. It is due to contraction of smooth muscle
T c. Increases heat production
T d. Center is located in the hypothalamus
F e. Is only activated in febrile condition

Q. 19. **Regarding body temperature**
T a. A core temperature of 43°C signifies a danger to life
T b. Newborn produces heat mainly by brown fat metabolism
T c. Insensible heat loss occurs via evaporation
T d. Temperature is distributed throughout the body via blood
T e. Central thermoreeeptor is located in the thalamus.

16
Nervous System

Nervous System

Nervous sytem is the most important organisation which control and integrates the different body functions and maintains the constancy of internal environment despite of extreme change in external environment.

Importance of nervous system :

1. It is the first appearing control system of the body.
2. It controls the rapid and first activities of the body e.g. muscular activity, secretion of glands etc.
3. It has regulatory effect upon endocrine system.
4. It helps in adustment of the body with the external environment.

Organization of the nervous system

The nervous system is unique in the vast complexity of thought processes and control actions it can perform. It receives literally millions of bits of information from the different sensory organs and then integrates all these to determine the responses to be made by the body.

General design of the nervous system :

i. *The central nervous system neuron (the basic functional unit)* : The central nervous system contains more than *100 billion* neurons.

   a. The *incoming signals* enter the neuron through synapses mainly on the neuronal dendrites, but also on the cell body. For different types of neurons, there may be only a few hundred or as many as *200,000* such *synaptic* connections from the input fibers.
   b. The *output signal* travels by way of a single axon leaving the neuron, but this axon has many separate branches to other parts of the nervous system or peripheral body.

   A special feature of most synapses is that the signal normally passes only in the forward direction (from axon to dendrites). This allows the signal to be conducted in the required directions for performing necessary nervous functions. We shall also see that the neurons are arranged into a multitude of differently organized neural networks that determine the functions of the nervous system.

ii. *Sensory division of the nervous system (sensory receptors)* : Most activities of the nervous system are initiated by sensory experience emanating from sensory receptors, whether visual receptors in the eyes, auditory receptors in the ears, tactile receptors on the surface of the body, or other kinds of receptors. This sensory experience can cause an immediate reaction from the brain, or memory of the experience can be stored in the brain for minutes, weeks, or years and determine bodily reactions at some future date.

   This information *enters the central nervous system* through the peripheral nerves and is conducted immediately to multiple sensory areas in the -

   a. Spinal cord at all levels
   b. Reticular substance of the medulla, pons, and mesencephalon
   c. Cerebellum
   d. Thalamus
   e. Areas of the cerebral cortex.

   Then, from the sensory areas, secondary signals are relayed to essentially all other parts of the nervous system.

iii. *Motor division (the effectors)* : The most important eventual role of the nervous system is to control the various bodily activities. This is achieved by controlling-

   a. Contraction of appropriate skeletal muscles throughout the body.
   b. Contraction of smooth muscle in the internal organs.
   c. Secretion by both exocrine and endocrine glands in many parts of the body.

   These activities are collectively called motor functions of the nervous system, and the muscles and glands are called effectors because they perform the functions dictated by the nerve signals.

   The skeletal muscles can be controlled from many levels of the central nervous system, including the-

   a. Spinal cord
   b. Reticular substance of the medulla, pons, and mesencephalon
   c. Basal ganglia
   d. Cerebellum
   e. Motor cortex.

   Each of these areas plays its own specific role, the lower regions being concerned primarily with automatic, instantaneous motor responses of the body to sensory stimuli, and the higher regions with deliberate movements controlled by the thought process of the cerebrum.

iv. *Processing of information- integrative; function of the nervous system* : One of the most important functions of the nervous system is to process incoming information in such a way that appropriate mental and motor responses will occur. More than 99 per cent of all sensory information is discarded by the brain as irrelevant and unimportant. For

instance, one is ordinarily unaware of the parts of the body that are in contact with clothing, as well as of the seat pressure when sitting. Likewise, attention is drawn only to an occasional object in one's field of vision, and even the perpetual noise of our surroundings is usually relegated to the subconscious.

v. *Storage of information-memory* : Only a small fraction of the important sensory information causes an immediate motor response. Much of the remainder is stored for future control of motor activities and for use in the thinking processes. Most of this information storage occurs in the *cerebral cortex*, but even the *basal regions of the brain* and the *spinal cord* can store small amounts of information. The storage of information is the process we call memory

vi. *Major levels of central nervous system function* : Three major levels of the central nervous system have specific functional attributes :

a. *Spinal cord level* : We often think of the spinal cord as being only a conduit for signals from the periphery of the body to the brain or in the opposite direction from the brain back to the body. This is far from the truth. Even after the spinal cord has been cut in the high neck legion many highly organized spinal cord functions still occur. For instance, neuronal circuits in the cord can cause -

1. Walking movements.
2. Reflexes that withdraw portions of the body from painful objects.
3. Reflexes that stiffen the legs to support the body against gravity.
4. Reflexes that control local blood vessels, gastrointestinal movements and reflexes that control urinary excretion.

In fact, the upper levels of the nervous system often operate not by sending signals directly to the periphery of the body but by sending signals to the control centers of the cord, simply *commanding* the cord centers to perform their functions.

b. *Lower brain or subcortical level* : Many, if not most, of what we call subconscious activities of the body are controlled in the lower areas of the brain-in the medulla, pons, mesencephalon, hypothalamus, thalamus, cerebellum, and basal ganglia.

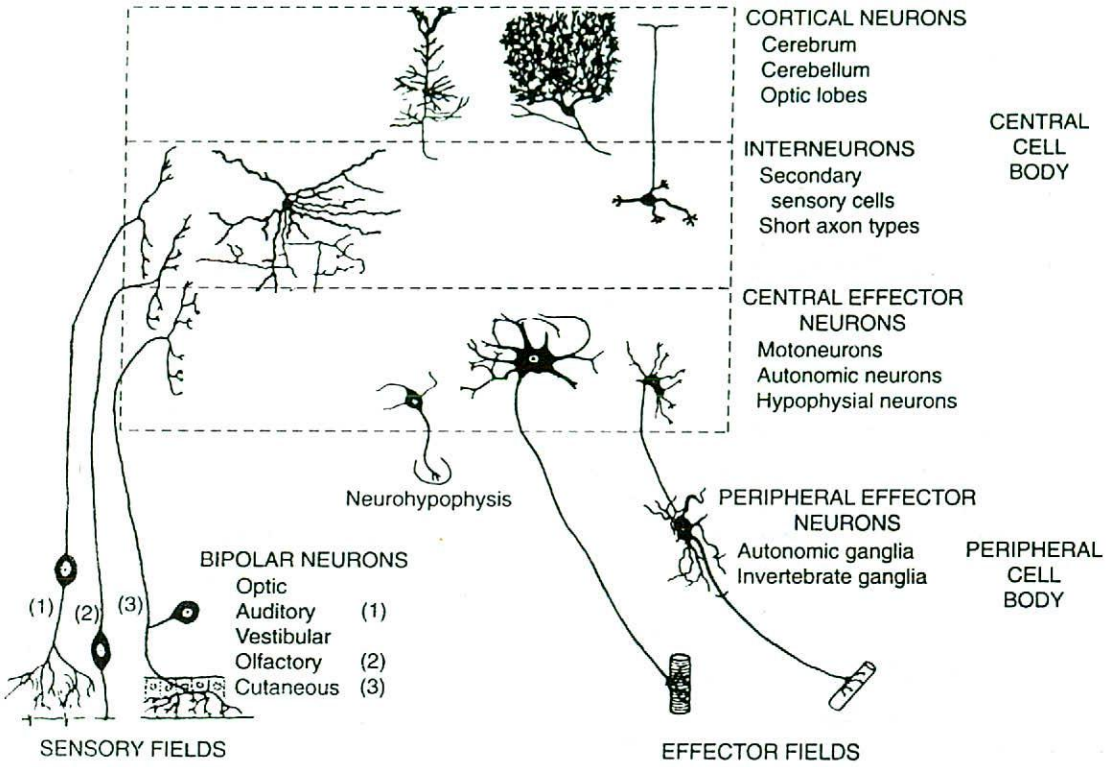


Fig. 16-1. *Some of the types of neurons in the mammalian nervous system.*

1. Subconscious control of arterial pressure and respiration is achieved mainly in the medulla and pons.
2. Control of equilibrium is a combined function of the older portions of the cerebellum and the reticular substance of the medulla, pons, and mesencephalon.
3. Feeding reflexes, such as salivation in response to the taste of food and the licking of the lips are controlled by areas in the medulla, pons, mesencephalon, amygdala, and hypothalamus.
4. Many emotional patterns, such as anger, excitement, sexual response, reaction to pain, and reaction to pleasure, can occur in animals after destruction of the cerebral cortex.

c. *Higher brain or cortical level* : Cerebral cortex is an extremely large memory storehouse. The cortex never functions alone but always in association with lower centers of the nervous system.

Without the cerebral cortex, the functions of the lower brain centers are often imprecise. The vast storehouse of cortical information usually converts these functions to determinative and precise operations.

Finally, the cerebral cortex is essential for most of our thought processes, but it cannot function by itself in this. In fact, it is the lower brain centers, not the cortex, that initiate *wakefulness* in the cerebral cortex, thus opening its bank of memories to the thinking machinery of the brain.

(Ref. Guyton & Hall 11th Edition; page 555-558)

Classification of nervous system

1. *Central nervous system* :
   a. Brain :
      i. Fore brain : cerebrum and diencephalons
      ii. Midbrain
      iii. Hind brain : pons, medulla oblongata, cerebellum
   b. Spinal cord :
      Cervical segments 8
      Thoracic segments 12
      Lumber segments 5
      Sacral segments 5
      Coccygeal segments 1.
2. *Perepheral nervous system* : (***somatic and autonomic***)
   i. Spinal nerves and their ganglia (31 pairs) :
      a. Cervical 8
      b. Thoracic 12
      c. Lumber 5
      d. Sacral 5
      e. Coccygeal 1.
   ii. Cranial nerves and their ganglia (12 pairs).

Autonomic nervous system

Introduction

The autonomic nervous system, like the somatic nervous system, is organized on the basis of the reflex arc. Impulses initiated in visceral receptors are relayed via afferent autonomic pathways to the CNS, integrated within it at various levels, and transmitted via efferent pathways to visceral effectors. This organization deserves emphasis because the functionally important afferent components have often been ignored.

(Ref. Ganong 22th edition; page 223)

General function of autonomic nervous system

I. *Functions of sympathetic system* :
   a. Generally prepares the body for action by increasing -
      i. Respiration
      ii. Blood pressure
      iii. Haert rate
      iv. Blood flow to the skeletal muscles.
   b. Dilating pupils of the eye.
   c. Generally slowing down the vsisceral function.

I. *Functions of parasympathetic system* :
   a. Functionally antagonistic to the sympathetic system by decreasing -
      i. Respiration
      ii. Blood pressure
      iii. Haert rate
      iv. Blood flow to the skeletal muscles.
   b. Constricting the pupils of the eye.
   c. Generally increasing the actions and functions of visceral system.

Thus the parasympathetic brings about the homeostasis.

Division of the autonomic nervous system :

a. *Anatomical division* :
   i. Sympathetic division
   ii. Parasympathetic division.
b. *Chemical divisions* :
   i. *Cholinergic division* :
   ii. *Noradrenergic division.*

(Ref. Ganong 22th edition; page 223, 224)

Anatomic organization of autonomic outflow

The peripheral motor portions of the autonomic nervous system are made up of

i. *Preganglionic neurons* :
   a. *Cell bodies* : The cell bodies of the preganglionic neurons are located in the visceral efferent intermediolateral gray column of the spinal cord on the homologous motor nuclei of the cranial nerves.
   b. *Axons* : Their axons are mostly mydinated, relatively slowly conducting B fibers.

ii. *Postganglionic* neurons : The *axons* synapse on the cell bodies of postganglionic neurons that are located in all cases outside the CNS. The axons of the postganglionic neurons, mostly unmyelinated C fibers, end on the visceral effectors.

Each *preganglionic* axon diverges to an average of eight or nine *postganglionic* neurons. In this way, autonomic output is diffused.

Anatomically, the autonomic outflow is divided into two components : the *sympathetic* and *parasympathetic* divisions of the autonomic nervous system. In the gastrointestinal tract, these both communicate with the *enteric nervous system*, and this is sometimes called a ***third division*** of the autonomic nervous system.

(Ref. Ganong 22th Edition; page 223)

Table 13-2. **Responses of effector organs to autonomic nerve impulses and circulating catecholamines.**

Effector Organs	*Cholinergic impulse response*	*Noradrenergic Impulses*	
		Receptor type[2]	*Response*
Eyes			
Radial muscle of iris	...	α_1	Contraction (mydriasis)
Sphincter muscle of iris	Contraction (miosis)	...	...
Ciliary muscle	Contraction for near vision	β_2	Relaxation for far vision
Heart			
S-A node	Decrease in heart rate, vagal arrest	β_1, β_2	Increase in heart rate
Atria	Decrease in contractility and (usually) increase in conduction velocity	β_1, β_2	Increase in contractility and conduction velocity
A-V node	Decrease in conduction velocity	β_1, β_2	Increase in conduction velocity
His-Purkinje system	Decrease in conduction velocity	β_1, β_2	Increase in conduction velocity
Ventricles	Decrease in contractility	β_1, β_2	Increase in contractility
Arterioles			
Coronary	Dilation	α_1, α_2	Constriction
		β_2	Dilation
Skin and mucosa	Dilation	α_1, α_2	Constriction
Skeletal muscle	Dilation	α_1	Constriction
		β_2	Dilation
Cerebral	Dilation	α_1	Constriction
Pulmonary	Dilation	α_1	Constriction
		β_2	Dilation
Abdominal viscera	...	α_1	Constriction
		β_2	Dilation
Salivary glands	Dilation	α_1, α_2	Constriction
Renal		α_1, α_2	Constriction
		β_1, β_2	Dilation
Systemic veins	...	α_1, α_2	Constriction
		β_2	Dilation
Lungs			
Bronchial muscle	Contraction	β_2	Relaxation
Bronchial glands	Stimulation	α_1	Inhibition
		β_2	Stimulation

(Ref. Ganong 21th Edition; page-229)

Table 13-2. **Responses of effector organs to autonomic nerve impulses and circulating catecholamines.**

Effector Organs	*Cholinergic impulse response*	*Noradrenergic impulses*	
		Receptor type[2]	*Response*
Stomach			
Motility and tone	Increase	$\alpha_1, \alpha_2, \beta_2$	Decrease (usually)
Sphincters	Relaxation (usually)	α_1	Contraction (usually)
Secretion	Stimulation	α_2	Inhibition
Intestine			
Motility and tone	Increase	$\alpha_1, \alpha_2, \beta_1, \beta_2$	Decrease (usually)
Sphincters	Relaxation (usually)	α_1	Contraction (usually)
Secretion	Stimulation	α_2	Inhibition
Gallbladder and ducts	Contraction	β_2	Relaxation
Urinary bladder			
Detrusor	Contraction	β_2	Relaxation (usually)
Trigone and sphincter	Relaxation	α_1	Contraction
Ureters			
Motility and tone	Increase (?)	α_1	Increase (usually)
Uterus	Variable[3]	α_1	Contraction (pregnant)
		β_2	Relaxation (pregnant andnonpregnant)
Male sex organs	Erection	α_1	Ejaculation
Skin			
Pilomotor muscles	...	α_1	Contraction
Sweat glands	Generalized secretion	α_1	Slight, localized secretion
Spleen capsule	...	α_1	Contraction
		β_2	Relaxation
Adrenal medulla	Secretion of epinephrine and norepinephrine	...	...
Liver	...	α_1, β_2	Glycogenolysis
Pancreas			
Acini	Increased secretion	α	Decreased secretion
Islets	Increased insulin and glucagon	α_2	Decreased insulin and glucagon secretion
		β_2	Increased insulin and glucagon secretion
Salivary glands	Profuse, watery secretion	α_1	Thick, viscous secretion
		β	Amylase secretion
Lacrimal glands	Secretion	α	Secretion
Nasopharyngeal glands	Secretion		...
Adipose tissue	...	$\alpha_1, \beta_1, \beta_3$	Lipolysis
Juxtaglomerular cells	...	β_1	Increased renin secretion
Pineal gland	...	β	Increased melatonin synthesis and secretion

(Ref. Ganong 21th Edition; page-230, 231)

Q. 02. **Give the difference between preganglionic and postganglionic neurons.**

Ans. Differences between preganglionic and postganglionic neurons :

Preganglionic neuron	*Postganglionic neuron*
a. Cell body is situated in the lateral gray column of the spinal cord and in the cranial nerve nuclei.	a. Cell body is situated in a ganglion (peripheral ganglion) outside the CNS.
b. The nerve fibres are myelinated.	b. The nerve fibres are unmyelinated.
c. Usually the fibres are long.	c. Usually the fibres are short.
d. Nerve endings act by liberating acetylcholine.	d. Nerve endings act by liberating adrenaline, noradrenaline or acetylcholine.

Table -2. ***Fast and slow responses of postganglionic neurons in sympathetic ganglia.***

Potential	*Duration*	*Mediator*	*Receptor*
Fast EPSP	30 ms	Acetylcholine	Nicotinic cholinergic
Slow IPSP	2 s	Dopamine	D_2
Slow EPSP	30 s	Acetylcholine	M_2 cholinergic
Late slow EPSP	4 mm	GnRH	GnRH

(Ref. Ganong 22th Edition; page226)

Anatomical autonomic outflow

Anatomically, the autonomic outflow is divided into two components :

i. Sympathetic
ii. Parasympathetic.

In the gastrointestinal tract, these both communicate with the *enteric nervous system*, and this is sometimes called a third division of the autonomic nervous system.

(Ref. Ganong 22th edition; page 223)

Sympathetic division : The axons of the sympathetic preganglionic neurons leave the spinal cord with the ventral roots of the first thoracic to the third or fourth lumbar spinal nerves.

i. They pass via the ***white rami communicantes*** to the ***paravertebral sympathetic ganglion chain***, where most of them end on the cell bodies of the postganglionic neurons.
ii. The axons of some of the postganglionic neurons pass to the viscera in the various sympathetic nerves. Others reenter the spinal nerves via the ***gray rami communicantes*** from the chain ganglia and are distributed to autonomic effectors in the areas supplied by these spinal nerves.
iii. The postganglionic sympathetic nerves to the head originate in the ***superior***, ***middle***, and ***stellate ganglia*** in the cranial extension of the sympathetic ganglion chain and travel to the effectors with the blood vessels.
iv. Some preganglionic neurons pass through the paravertebral ganglion chain and end on postganglionic neurons located in ***collateral ganglia*** close to the viscera.
v. Parts of the uterus and the male genital tract are innervated by a special system of ***short noradrenergic neurons*** with cell bodies in ganglia in or near these organs, and the preganglionic fibers to these postganglionic neurons presumably go all the way to the organs.

(Ref. Ganong 22th edition; page 223)

Transmission in sympathetic ganglia

At least in experimental animals, the responses produced in postganglionic neurons by stimulation of their preganglionic innervation include-

i. A rapid depolarization (fast EPSP) that generates action potentials
ii. A prolonged inhibitory postsynaptic potential (slow IPSP)
iii. A prolonged excitatory postsynaptic potential (slow EPSP)
iv. A late slow EPSP.

The late slow EPSP is very prolonged, lasting minutes rather than milliseconds. These slow responses apparently modulate and regulate transmission through the sympathetic ganglia. The initial depolarization is produced by acetylcholine via a nicotinic receptor. The slow IPSP is probably produced by dopamine, which is secreted by an *interneuron* within the ganglion. The interneuron is excited by activation of an M_2 muscarinic receptor. The interneurons that secrete dopamine are the small, intensely *fluorescent cells (SIF cells)* in the ganglia. The production of the slow IPSP does not appear to be mediated via cAMP, suggesting that a D_2 receptor is involved. The slow EPSP is produced by acetylcholine acting on a muscarinic receptor on the membrane of the postganglionic neuron. The late slow EPSP is produced by GnRH or a peptide closely resembling it.

(Ref. Ganong 22th Edition; page224)

Parasympathetic division :

i. *Cranial outflow* : The cranial outflow of the parasympathetic division supplies the visceral structures in the head via the oculomotor, facial, and glossôpharyngeal nerves, and those in the thorax and upper abdomen via the vagus nerves.

ii. *Sacral outflow* : The sacral outflow supplies the pelvic viscera via the pelvic branches of the second to fourth sacral spinal nerves.

The preganglionic fibers in both outflows end on short postganglionic neurons located on or near the visceral structures.

(Ref. Ganong 22th Edition; page223)

Q. 02. **Give the location of parasympathetic preganglionic and postganglionic neurons.**

Nerve	*Parasympathetic preganglionic neurons*	*Parasympathetic postganglionic neurons*
i. ***Cranial*** :		
Ocolomotor nerve	Edinger-Westphal nucleus in the mid brain	Cilliary ganglion
Facial nerve	Superior salivatory nucleus in the medulla oblongata	Sub-mandibular and pterygopalatine ganglia.
Glossopharyngial nerve	Inferior salivatory nucleus in the medulla oblongata	Otic ganglia
Vagus nerve	Dorsal nucleus of vagus in the medulla oblongata	Thoraeic and abdominal autonomic plexuses, close to or within the viscera supplied.
ii. ***Sacral*** : S-2, 3, 4	Anterior horn cells of the gray column of sacral segment of spinal cord.	Minute ganglia in the walls of pelvic viscera supplied.

Q. 02. **How do the sympathetic and parasympa- thetic divisions of the autonomic nervous system differ functionally?**

Ans. Functional differences between sympathetic and parasympathetic system :

Sympathetic	*Parasympathetic*
a. Prepares the body for defence in emergency.	a. Serves to comfort the body by promoting the orderly processes of the body.
b. Widespread function due to many postganglionic fibres and liberation of epinephrine and norepinephrine from suprarenal medulla.	b. Discrete action with few postganglionic fibres.
c. Catabolic function, mobi lizes body energies for dealing with increase in activity.	c. Anabolic function, conserves body energies.
d. Generally vasoconstrictor and raises blood pressure	d. Generally vasodilator, and lowers blood pressure
e. Accelerates heart rate, increases blood pressure, general constriction of cutaneous arteries thus causing increased blood supply to heart, muscle and brain.	e. Slows the heart(decreased heart rate decreases blood pressure). General vasodilator.
f. Provides a wider field of vision by dilating the pupil of the eye.	f. Constricts the pupil
g. Slows down peristalsis	g. Increases glandular and peristaltic activities.
h. Causes constriction of the sphincter except the sphincter pupillae.	h. Causes dilatation of the sphincter except the sphincter pupillae.

Chemical autonomic division

Chemical divisions of the autonomic nervous system : On the basis of the chemical mediator released, the autonomic nervous system can be divided into-

i. ***Cholinergic division*** : The neurons that are cholinergic are-
   a. All preganglionic neuron
   b. Anatomically parasympathetic postganglionic neurons
   c. Anatomically sympathetic postganglionic neurons which innervate sweat glands
   d. Anatomically sympathetic neurons which end on blood vessels in skeletal muscles and produce vasodilation when stimulated (sympathetic vasodilator nerves).

ii. ***Noradrenergic division*** : The remaining postganglionic sympathetic neurons are noradrenergic or, apparently, adrenergic in the case of the ICA cells.

The adrenal medulla is essentially a sympathetic ganglion in which the postganglionic cells have lost their axons and secrete norepinephrine, epinephrine, and some dopamine directly into the bloodstream.

The cholenergic preganglionic neurons to these cells have consequently become the secretomotor nerve supply of this gland. *(Ref. Ganong 22th Edition; page224)*

Chemical transmission of autonomic nervous system

Transmission at the synaptic junctions between pre and postganglionic neurons and between the postganglionic neurons and the autonomic effectors is chemically mediated the principal transmitter agents involved are *acetylcholine* and *norepinephrine*, although dopamine is also secreted by interneurons in the sympathetic ganglia and *GnRH* is secreted by some of the preganglionic neurons. GnRH mediates a slow excitatory response. In addition, there are cotransmitters in autonomic neurons; for example, VIP is released with acetylcholine, and ATP and neuropeptide Y with norepinephrine. VIP causes bronchodilation, and there may be a separate VIP secreting nonadrenergic noncholinergic nervous system innervating bronchial smooth muscle.

(Ref. Ganong 22th Edition; page223)

Neuron

A nerve cell with all its processes is called neuron.

Neuron is the structural and functional unit of nervous system. It consists of cell body or soma and two types of processes- axon and dendrite.

Zones of the neurons

Neurons generally have four important zones :

1. *Receptor or dendritic zone* : Where multiple local potential charges generated by synaptic connections are integrated.
2. *Action potential generated zone* : A site where propagated action potentials are generated i.e.
   a. The initial segment in spinal motor neurons.
   b. The initial node of Ranvier in cutaneous sensory neurons.
3. *Impulse propagation zone* : An axonal process that trnsmits propagated impulses to the nerve endings.
4. *Nerve endings* : Where action potential causes the release of synaptic transmitters.

The cell body is often located at the dendritic zone end of the axon, but it can be within the axon (i.e auditory neurons) or attatched to the side of the axon i.e cutaneous neurons. Its location makes no difference as far as the receptor function of the dendritic zone and transmission function of the axon are concerned.

It should be noted that integration of passive electrical activity is not the only function of dendrities, and flactuations in the sensitivity of individual dendrites alter their responses. Some nearons in the CNS have no axons, and local potentials pass from one dendrite to another. In other situations in the cortex, there is evidence for active as well as passive electrical responses to stimulation of dendrites.

(Ref. Ganong 22th edition)

Total number of neuron : 100 billion (about)

Dimensions of neurons : Spinal neuron supplying the muscles of foot, for example it has been calculated that if the cell body were the size of a tennis ball, the dendrities of the cell would fill an average sized living room and the axon would be upto 1.6 km (almost a mile) long although only 13 mm (0.5 inch) in diameter.

(Ref. Ganong 22th edition)

Function of neuron : Neuron is responsible for reception, conduction, integration and transmission of nerve impulse.

Classification of neuron

A. *According to number of processes :*
   i. *Unipolar :* Posseses a single process.
      Example : Only in foetus and lower vertebrae.
   ii. *Bipolar :* Here two processes present - One is axon and other is dendrite.
      Example : Inner nuclear layer of the retina and VIIIth cranial nerve nucleus.
   iii. *Pseudounipolar :* Pseudo means false. Originally these are bipolar but inturn two process fused into one which further divides into two. Ex : Present in dorsal root ganglia.
   iv. *Multipolar :* Posseses one axon and several dendrites.
      Ex : Pyramidal cell of cerebral cortex.

B. *According to function :*
   i. *Motor or efferent :* It carry impulse away from the cell body.

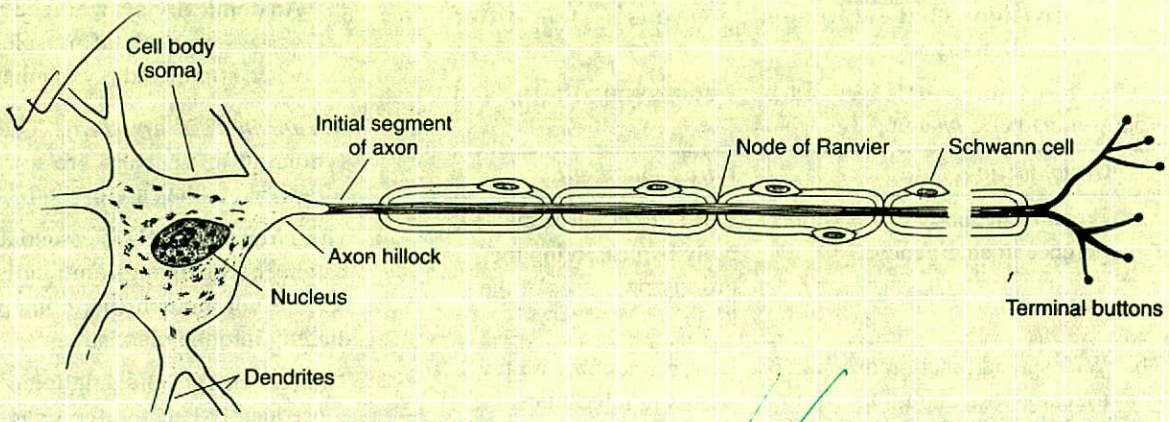


Fig. 16-2. *Motor neuron with myelinated axon*

ii. *Sensory or afferent :* It carry impules towards the cell body.

C. *According to position :*

i. *Upper Motor neuron :* Pyramidal cells and its axon is called upper motor neuron.

ii. *Lower motor neuron :* Anterior horn cells and its axon is called lower motor neuron.

D. *According to the length of the axon :*

i. *Golgi type I :* Contains very long axon that passes out the side of the grey matter and enters into the white matter.

ii. *Golgi type II :* Axon is short that does not leave the grey matter.

Resting membrane potential :

1. Large nerve fibers : -90 millivolts
2. Neural soma : -65 millivolts
3. Neurons : -70 millivolts.

Difference between axon and dendrite :

Axon	*Dendrite*
1. It carries impulse away from cell body.	1. It carries impulse toward the cell body.
2. It is single in each neuron.	2. Several in number from nill to many.
3. Generally long.	3. Generally short.
4. Usually unbranched.	4. Usually branched.
5. Histologically Nissle granules are absent.	5. Nissle granules are present.
6. Arises from axon hillock.	6. Arises from any part of the soma of the neuron.

Motor neuron

a. *Definition* : Motor neuron carries motor impulses from the CNS to the effector organs.

b. *Function* : Motor neurons are involved in :

i. Glandular secretion

ii. Muscular contraction

iii. Cardiac rates and respiratory movements.

c. *Types* : Two sets of motor neurons are involved to execute a motor function that are planned in motor cortex :

i. ***Upper motor neurons*** : The neurons in the brain and spinal cord that activate the motor neurons.

Effect of lesions :

a. Spastic paralysis

b. Hyperactive stretch reflexes

c. Absence of muscle atrophy.

However, there are three types of upper motor neurons to consider. Lesions in many of the posture-regulating pathways cause spastic paralysis, but lesions limited to the corticospinal and corticobulbar tracts produce weakness (paresis) rather than paralysis, and the affected musculature is generally hypotonic. Cerebellar lesions produce incoordination. The unmodified term upper motor neuron is therefore confusing.

ii. ***Lower motor neurons*** : The spinal and cranial motor neurons that directly innervate the muscles.

Effect of lesions :

a. Flaccid paralysis

b. Muscular atrophy

c. Absence of reflex responses.

(Ref. Ganong 22th edition; page 203)

Q. 00. **What are the differences between upper and lower motor neuron lesion?**

Ans. Differences between upper and lower motor neuron lesion :

Upper motor lesion :	*Lower motor lesion*
1. In upper motor neuron lesion paralized muscles are rigid due to increase muscle tone.	1. In upper motor neuron lesion paralized muscles become flaccid due to loss of muscle tone.
2. In upper motor neuron lesion deep reflexes are exaggerated & superficial reflexes lost.	2. In lower motor neuron lesion both superficial and deep reflexes lost.
3. In upper motor neuron lesion muscles are not wasted.	3. In lower motor neuron lesion muscles are degenerated & undergo wasting.
4. In upper motor neuron lesion Babinski sign positive.	4. In lower motor neuron lesion Babinski sign negative.

(Ref. Ganong 22th edition; page-203)

Q. 01. **Briefly describe the action potential of a neuron?**

Ans. Resting membrane potential of a neuron is usually about -70 mV.

A slight decrease in resting membrane potential leads to increased K^+ efflux and Cl^- influx restoring the resting membrane potential. However, when depolarization exceeds 7 mV, the voltage-gated Na^+ channels start to open at an increased rate (Na^+ channel activation), and when the firing level is reached, the influx of Na^+ along its inwardly directed concentration and electrical gradients is so great that it temporarily swamps the repolarizing forces.

The increase in Na^+ conductance is short-lived. The Na^+ channels rapidly enter a closed state called the inactivated state and remain in this state for a few milliseconds before returning

to the resting state. In addition, the direction of the electrical gradient for Na^+ is reversed during the over shoot because the membrane potential is reversed, and this limits Na^+ influx. A third factor producing repolarization is the opening of voltage-gated K^+ channels. This opening is slower and more prolonged than the opening of the Na^+ conductance. The net movement of positive charge out of the cell due to K^+ efflux at this time helps complete the process of repolarization. The slow return of the K^+ channels to the closed state also explains the after-hyperpolarization.

Althogh Na^+ enters the nerve cell and K^+ leaves it during the action potential, the number of ions involved is minute relative to the total numbers present. The fact that the nerve gains Na^+ and loses K^+ during activity has been demonstrated experimentally, but significant differences in ion concentrations can be measured only after prolonged, repeated stimulation.

The slower opening and delayed closing of the voltage-gated K^+ channels also explain accommodation. If depolarization occurs rapidly, the opening of the Na^+ channels overwhelms the repolarizing forces, but if the induced depolarization is produced slowly, the opening of K^+ channels balances the gradual opening of Na^+ channels, and an action potential does not occur.

A decrease in extracellular Ca^{++} concentration increases the excitability of nerve and muscle cells by decreasing the amount of depolarization necessary to initiate the changes in the Na^+ and K^+ conductance that produce the action potential. Conversely an increase in extracellular Ca^{++} concentration stabilizes the membrane by decreasing excitability.

(Ref. Ganong 22th Edition; Page 59)

Degenaration of neuron

a. *Definition :* The sum total destructive changes that happen to a nerve fibre after its injury or complete transection is called degeneration.

b. *Types of degeneration :* Degeneration are of two types-
   i. Retrograde degeneration : The degeneration that affect the cell body and proximal part of the cut fibre.
   ii. Wallerian degeneration : Degenerative changes that affect the distal part of the cut fibre.

c. *Causes of degeneration :*
   i. Transection of nerve fibre.
   ii. Crushing of nerve fibre.
   iii. Local injection of toxic substance.
   iv. Interference with blood supply.

(Ref. Wright's)

Changes take place after transection of a neuron

After transection nerve fibre degeneration takes place at two levels-

A. ***Retrograde degeneration*** :
   1. *Early change : Within 24 hours :*
      a. Nissle granules begins to disintegrate.
      b. Fragmentation and disintegration of Golgi apparatus & mitochondria.
      c. Cell body becomes spherical (due to imbibation of water.)
      d. Neurofibrin becomes tortuous and fragmented.
      e. Nucleus pushed to the periphery.
      f. Cell membrane shows degenerative change.
   2. *Late change :*
      a. Disappearance of Nissle granules, Golgi apparatus, neurofibril and endoplasmic reticulum.
      b. Chromatolysis : The above changes in the cell body and extrusion of the nucleus is known as chromatolysis.

B. ***Wallerian degeneration :***
   1. *Early changes : Within 24 hours :*
      a. Axon become swollen, neurofibrils become wavy, tortuous, granular and ultimately fragments out.
      b. Axon divides into numerous twisted segments.
      c. Myelin sheath degenerates.
      d. Schwann cells of neurolemal sheath shows proliferative change.
   2. *Late changes :*
      a. All the histological changes are intensified.
      b. The endoplasmic reticulum and plasma membrane disappear.
      c. Myelin sheath breaks into myelin drops and disappear.
      d. Invasion of macrophages that removes cellular debris.

Neuroglia

a. *Definition :* These are the non-excitable supporting connective tissues present in nervous system, called neuroglia.

b. *Classification of neuroglia :*
   1. Microglia
   2. Macroglia
      a. Astrocyte
      b. Oligodendrocyte
         i. Fibrous
         ii. Protoplasmic
      c. Glioblast.

c. *Functions of neuroglia :*
   i. Supporting
   ii. Insulation
   iii. Phagocytosis
   iv. Formation of myelin sheath.

Myelinogenesis

The process of formation and deposition of myelin sheath around a nerve fibre is called myelinogenesis.

Process of myelination :

i. *In peripheral nerve fibre :* Myelinogenesis begins with the growing of Schwann cell around the axon. The axon is first enveloped completely by the Schwann cell membrane. The Schwann cell membrane then gives several turns leaving the axon surrounded by many concentric layers. The cytoplasm disappear from this concentric layer. The compact myelin sheath consist of several concentric layer of Schwann cell membrane. The Schwann cell membrane consist of outer and inner layers of protein separated by a layer of lipid - sphingomyelin that act as a insulator. The myelin sheath over the axon are interrupted by constriction called node of Ranvier.

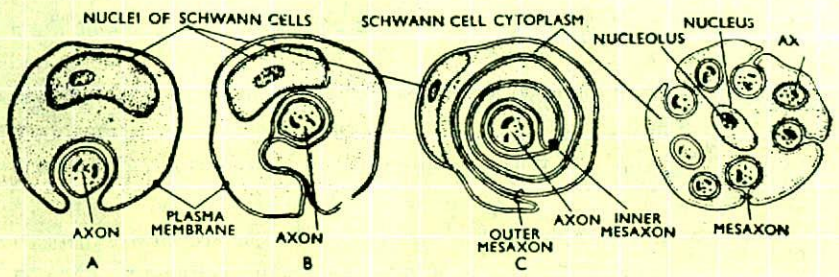


Fig. 16-3.Diagramatic representation of the process of myelination.

ii. *In CNS :* Myelinogenesis occured by the oligodendroglia similar to that of Schwann cell.

Nerve fibre

Definition : A nerve fibre is simply the long process of neuron which conduct nerve impulse.

Each nerve fibre has a central core of cytoplasm called axoplasm, surrounded by an outer membrane axolema. Axoplasm and axolema are collectively called axon cylinder.

Structure of a myelinated nerve fibre

Nerve fibre which is covered by myelin sheath is called myelinated fibre. A myelinated nerve fibre consist of following structures from within outwards-

i. *Axoplasm :* A central core of semifluid which flows from the cell body to the periphery. Axoplasm contains fibrilar components which run parallel to the axis of the fibre. Mitochondria and endoplasmic reticulum also present in it.

ii. *Axolema :* A membrane surrounding the axoplasm and separates it from surrounding structures.

iii. *Myelin sheath :*A sheath of phospholipid material outer to axolema which is a specialized set of Schwann cell membrane.

4. *Neurolema :* The outer most layer of a myelinated nerve.

(Ref. Wright's)

Properties of nerve fibre

1. *Excitability :*The nerve fibre can be stimulated by a stimulus of electrical, mechanical, chemical or thermal stimulus.
2. *Conductivity :* Nerve fibre can conduct impulse along both direction.
3. *Adaptation :* The nerve fibre quickly adapts itself. Due to this adaptation there is no excitation during the pasage of a constant current.
4. *Accomodation :* If a stronger stimulus is applied to a nerve very slowly there is no response due to lack of attaining threshold strength. This is accomodation.
5. *Infatiguability :* If a nerve fibre stimulated repeatedly, after a certain period it fails to give any response.
6. *All or none low :* If adequate stimulus is applied to a single nerve it will respone to its maximum.
7. *Summation :* In a nerve fibre summation of two submaximal stimuli is possible.

Calssification of nerve fibre

I. *According to the diameter and conduction velocity.*

Fiber type	*Diameter* mm	*Velocity of conduction* m/second	*Spike Duration* (ms)	*Absolute Refractory* peroid (ms)
A				
α	12-20	70-100		
β	5-12	30-70		
γ	3-6	15-30	0.4-0.5	0.4-1
δ	2-5	12-30		
B	<3	3-15	1.2	1.2
C				
Dorsal root	0.4-1.2	0.5-2	2	2
Sympathetic	0.3-1.3	0.7-2.3	2	2

N.B. *A and B fibers are myelinated; C fibers are unmyelinated.*

(Ref. Ganong 22th edition; page 61)

II. *Functionally :*
- i. Motor
- ii. Sensory.

III. *Histologically :*
- i. Myelinated
- ii. Un-myelinated.

IV. *Chemically :*
   i. Cholenergic : Producing acetylcholine
   ii. Adrenergic : Producing norepinephrin.

Numerical classification of sensory neuron

Numerical classification sometimes used for sensory neurons :

Number	*Origin*	*Fiber type*
Ia	Muscle spindle, annulo-spiral ending	Aα
Ib	Golgi tendon organ	Aα
II	Muscle spindle, flower spray ending touch, pressure	Aβ
III	Pain, and cold receptors; some touch receptors.	Aδ
IV.	Pain, temperature, and other receptors.	Dorsal root C

(Ref. Ganong 22th edition; page 61)

Relative susceptibility of mammalian A, B, C nerve fibers to conduction block produced by various agents.

Susceptibility to	*Most susceptible*	*Intermediate susceptible*	*Least susceptible*
Hypoxia	B	A	C
Pressure	A	B	C
Local anesthesia	c	B	A

(Ref. Ganong 22th edition; page 61)

Function of nerve fibre

I. A fiber :
   a. Aα fiber :
      i. Proprioception
      ii. Somatic motor.
   b. Aβ fiber :
      i. Touch
      ii. Pressure
      iii. motor.
   c. Aγ fiber :
      i. Motor to muscle spindle
   d. Aδ fiber :
      i. Pain
      ii. Cold
      iii. touch.

II. B fiber :
   i. Preganglionic autonomic.

III. C fiber :
   a. Dorsal root :
      i. Pain
      ii. Temperature
      iii. Some mechanoreception
      iv. Reflex responses.
   b. Sympathetic :
      i. Postgaglionic sympathetic.

(Ref. Ganong 22th edition; page 61)

Degree of neve injury

Sunderland's degree of injury :

a. *First degree injures* : These are pressure being applied to a nerve for a limited time thus occluding its blood supply and resulting in a local anoxia which impair the nerve function.

   In it, axon is not destroyed but merely losses its functional properties for a short time which returns within a few hours to few weeks.

b. *Second degree of injuries* : These are the results of prolonged and or severe pressure being exerted on some part of the nerve.

   Death of the axon at the site of pressure followed by the death of the axon distal to it, because the axon is separated from the cell body. Chromatolysis occurs in the cell body.

   Regeneration of axon is facilitated by the presence of uninterrupted endoneurial tubes.

c. *Third, fourth, and fifth degree injuries* : *Third degree* injuries are characterized by the endoneurial tubes becoming interrupted, *fourth degree* injuries by the fascicles becoming disorganized; and *fifth degree* injuries by the nerve trunk being severed.

(Ref. Wright's)

Spinal cord

1. *Anatomy* : The spinal cord is that part of CNS which is contained within the vertebral canal & is the prolongation of the brain.

2. *Development* : It developes from that portion of neural tube which lies caudal to the level of the 4th pair of somites.

3. *Lengths* : It is about 45 cm (18 inch) long & about 1.25 cm (0.5 inch) wide.

4. *Extention* : From the horizontal plane passing between the middle of the odontoid process of the 2nd cervical vertebra & the upper border of the posterior arch of the atlas & terminates below in a conical extremity, the *conus medullaris* at the lower border of the body of 1st lumbar vertebra.

5. *Enlargements* : It presents two enlargements - *cervical & lumber*. The *cervical enlargement* extends from the level of 3rd cervical to the 2nd thoracic segment of the spinal cord. From this enlargements nerves for the upper extremities emerge out.

   The lumbar enlargement extends from the ninth thoracic

vertebra to the twelfth thoracic vertebra. From it nerves for lower extremities emerge out.

6. *Filum terminale* : A delicate, thread like non-nervous filament, about 20 cms long. Extends from the lower end of conus medullaries and terminates by being attached to the dorsal aspect of first coccygeal vertebra.
7. *Coverings* : It has three coverings; from without inwards- dura mater, arachnoid mater & pia mater. The space between the arachnoid and pia mater is subarachnoid space which contain CSF and extends as down as the 2nd sacral vertebra.

Parts of spinal cord

On cross section, the spinal cord has two parts :

1. *Central- grey mater :* It is composed of a mass of nerve cells, nerve fibres consisting of both axons & dendrons together with a framework of neuroglial cells. It is divided into two symetrical halves which are connected by a transverse band, resemble the letter H. It has three column (horn)-
   a. Anterior horn
   b. Lateral horn (only in thoracic horn)
   c. Posterior horn.
2. *Peripheral- white matter :* It surrounds the grey matter and consists of nerve fibres & neuroglia. It appear as white because most of the fibre are myelinated.
3. *Central canal :* It exists through out the spinal cord and is continuous above with the inferior angle of 4th ventricle and below it expands as far down as 2" within filum terminale.

Functions of spinal cord

1. It is the main pathway for all incoming and outgoing impulses from the higher centre to the periphery & vice versa.
2. It is the main centre of reflex activites.
3. It exerts traphic control over the muscular system.

Spinal cord transection

a. *Causes of complete transection of spinal cord*
   i. Gun shut injury
   ii. Fracture, dislocation
   iii. Acute transverse myelitis.

b. ***Effects of complete transection of spinal cord***

The effects depend on the site of section.

I. *Above the 5th cervical segment* : The subject dies due to respirtatory failure or due to involvement of phrenic & intercostal nerves.

II. *Section between C_5-T_1* : The subject may survive with quadriplegia & the effects may be summarized in the following stages-

1. *Stage of spinal shock :* This stage follows immediately after the section & lasts for a variable time-
   a. Muscles are completely flaccid at and below the level of section and all the four limbs are paralized.
   b. Lack of responsiveness to stimulus below the section.
   c. All reflexes are lost except anal reflex.
   d. Sphincters are paralyzd.
   e. Retention of urine and faeces is present.
   f. Priapism (Persistent erection of penis) occurs, immediately after ingury.
   g. BP may or may not be effected.
2. *Stage of recovery or reflex activity :* After a variable time as the stage of shock passes off, depeding on the condition of the patient, functional activity appears; that is-
   a. Return of reflex tone,
   b. Involuntary movement,
   c. Return of reflex movement.
3. *Stage of failure of reflex activity.*

III. *Section at lumbar region :*
   i. Flaccid paralysis of lower limbs
   ii. Loss of all reflexes.

Causes of spinal shock : It is neither due to trauma nor due to fall of blood pressure. It is believed to be due to cutting off of the impulses from the higher centres which are excitatory to the spinal centres.

Effects of section of anterior root

1. *Functional changes* :
   a. Flaccid paralysis of the affected muscles.
   b. Loss of reflexes.
   c. Muscualr wasting.
   d. Reaction of degenaration present.
   e. Sympathetic paralysis.
2. *Degenarative changes* :
   a. Degenaration of peripheral portion.
   b. Degenaration of white rami communication upto sympathetic ganglion.
   c. Chromatolysis of anterior and lateral horn cells.

Effects of section of posterior root

1. *Functional changes :*
   a. Loss of all sensation.
   b. Incordinated movements of the muscles due to loss of kinaesthetic sensation.
   c. Loss of muscle tone and reflexes.
   d. Trophic ulcers due to loss of sensation.

e. Vasomotor disturbances due to degenaration of the antidromic vasodilator fibres.

2. *Degenarative changes :*
   a. If distal to the ganglion-
      i. Degenaration of the peripheral fibres upto the receptor organs.
      ii. Degenaration of the fibres of the recurrent sensibility.
      iii. Degenaration of the antidromic vasodilator fibres.
      iv. Chromatolysis of the ganglion cells.
   b. *If proximal to the ganglion* :
      i. Degenaration of tract of Gall & Burdach and of Lissauer & Comma (descending) tract upto the next neuron.
      ii. Chromatolysis of the ganglion cells.

Effects of hemisection of the spinal cord

Hemisection means section or lesion which involves one lateral half of spinal cord.

Effects :

i. *Degenartive change :*
   a. Cellular damage,
   b. Damage to fibres

ii. *Functional change :*
   a. Above the level of section
   b. At the level of section
   c. Below the level of section.

Degenarative change :

1. *Neural cell damage :*
   a. Damage to anterior horn cells lead to their destruction including the motor end plate and no regenaration occurs.
   b. Damage to posterior horn cells lead to degenaration of second neurons in the sensory pathway for pain and temperature sensation of same side.
   c. Damage to lateral horn cells lead to degenaration of the preganglionic viceromotor, pilomotor & vasomotor nerves.
2. *Damge to fibres :*
   a. Distal part of the divided fibres undergoes degenaration and involving the end-organs in connection with it.
   b. Proximal part of the fibre & the related nerve cells also degenarates for a variable extent.
   c. There may be associated transneuronal degenaration.

Functional change :

1. *Below the level of section :*
   a. *Same side :*
      i. Sensory change : Loss of fine touch, tactile localization, tactile discrimination and kinesthetic sensation due to the damage of tract of Gall and Burdach. But crude touch, pain and thermal sensation remain unchange.
      ii. Motor change : Extensive paralysis of upper motor type due to destruction of pyramidal tract.
   b. *Opposite side :*
      i. Sensory Change : Loss of touch, pain and thermal sensation due to damage of spinothalamic tract. But fine touch, tactile localization, tactile discrimination and Kinesthetic sensation remain unchanged.
      ii. Motor change : A few paralysis may occur.
2. *At the level of section :*
   a. *Same side :*
      i. Sensory change : Complete anesthetia due to destruction of posterior nerve root, posterior horn cell.
      ii. Motor change : Lower motor type of paralysis due to destruction of anterior horn cell.
   b. *Oppoisite side :*
      i. Sensory change : Some loss of pain sensation due to destruction of crossed horizontal spinothalamic tract.
      ii. Motor change : Nill or very slight because some direct fibres may injuried.
3. *Above the level of section :*
   a. *Same side* : Hyperaesthesia due to irritation of the upper cut end of the damaged fibre (possibly).
   b. *Opposite side* : Hyperasthesia may be referred.

Brown sequard syndrom

It is found that below the level of hemisection of spinal cord there is extensive sensory loss but little motor loss of opposite side and where in the same side there is extensive motor loss but little sensory loss. This phenomenon is known as Brown sequard syndrom.

Babinski sign

Normally scratching of the skin of the sole causes planter flexion of great toe. But in case of infants and pyramidal tract lesion at any level above the 1st sacral segment, this normal response is changed into dorsiflexion of great toe, with faning of other toes is called Babinski sign.

Synapse

Definition : Synapse is the junction between two neurons where one neuron ends and other neuron begins. It is the functional continuty between two neurons.

Functional anatomy of synapse : Before synapsing with a cell body or process the axon terminals of the presynaptic neuron enlarge called synaptic knob, terminal knobs, butons, or end-

feet. The membrane of the synaptic knob is called presynaptic membrane and that of the cell body or process of the post synaptic neuron is called postsynaptic membrane. Both these membrane are separated by synaptic cleft having a width

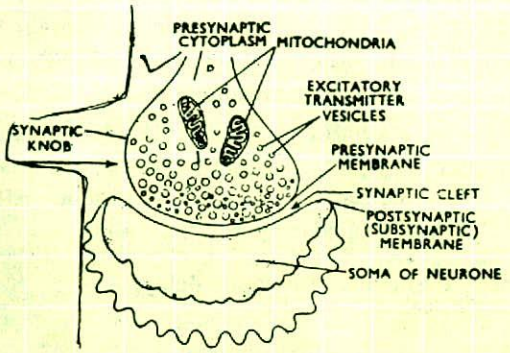


Fig. 16-4. Diagram of Synapse.

usually of 200-300 angstrom. The presynaptic knob contains numerous mitochondria and vesicles which contain neurotransmitter substances. The mitochondria supplies energy that is needed for the synthesis of the neurotransmitter substances.

Function of synapse :

1. Conduction or transmission of impulse.
2. Integration of impulse.
3. Formation of reflex arc.
4. Acts as a connection spot in neural chain.
5. Modulation of neural activity.

Classification of synapse

a. *According to structural organization :*
   i. *Axosomatic :* Axon of one neuron synapses with the cell body of other neuron.
   Example : Between the basket cell and purkinjee cell in the cerebellum.
   ii. *Axodendritic :* Axon of one neuron synapses with dendrite of other neuron. Ex. between the climbing fibres and the dendrite of the purkinjee cell.
   iii. *Axoaxonic :* Axon of one neuron synapses with axon of other neuron.

b. *According to the nature of neurotransmitter releases* :
   i. *Cholenergic synapse :* Releases acetyle choline.
   ii. *Adrenergic synapse :* Releases norepinephrine and epinephrine.

Properties of synapse

1. *One way conduction :* Synapse always conduct impulse one way that is from presynaptic neuron to the post synaptic neuron. It is due to present of abundant neurotransmitter in the presynaptic neuron.
2. *Synaptic delay :* It is the time taken by an impulse to cross the synapse. It is about 0.5 milli second.
   Cause :
   a. Delay in the release of neurotransmitters.
   b. Passing of neurotransmitters through the synaptic cleft.
   c. Delay in the combination of neurotransmitter with post synaptic receptors.
   d. Delay in the set up of action potential.
3. *Fatigue :* When a synapse is rapidly and repeatedly stimulated, the power of conduction of impulse will progressively become less, called fatigue of synapse. It is due to-
   i. Exhausness of neurotransmitter substances
   ii. Progressive inactivation of the receptor of the post synaptic neuron.
4. *Synaptic response :* Response to the impulse received by synapse may be similar or dissimilar. Sometime one neuron receives many impulse via synapse but it integrates and discharge its own.
5. *Inhibition :* It is an active process which either prevents the onset of activity in a structure or stops the activity already present. It may be direct, indirect, presynaptic, post synaptic and negative feed back inhibition.

Synaptic transmission : When an action potential arrives at the presynaptic terminal, it will depolarize the presynaptic membrane, causing opening of the Ca^{++} chanel and Ca^{++} from synaptic cleft enters into synaptic knob binds with receptor of presynaptic membrane. This Ca^{++} receptor binding causes the

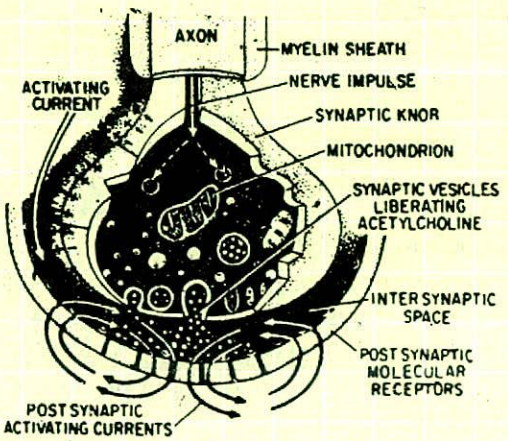


Fig. 16-5. Synaptic transmission.

vesicles bind with membrane, fuse with it and finally burst and neurotransmitter releases into synaptic cleft, passes through this cleft and binds with the specific receptors of the post synaptic membrane. The post synaptic membrane has Na^+, K^+ and CI^- chanel. The transmitter which open the Na^+ chanel are called excitatory and those which open the K^+ or CI^- chanel are called inhibitory impulse.

Q. 04. **What are the types of synaptic transmission?**

Ans. Types of synaptic transmission :

i. Chemical transmission
ii. Electircal transmission
iii. Both chemical and electrical transmission.

Characteristics of synaptic transmission : Some special characteristics of synaptic transmission are :

i. Summation :
   a. Spatial suntmation
   b. Temporal summation
ii. Synaptic delay
iii. Synaptic inhibition
   a. Direct inhibition
   b. Indirect inhibition
   c. Presynaptic inhibition
   d. Postsynaptic inhibition.
   e. Negative feed back inhibition.

Presynaptic neuron : Neuron which release neurotransmitters.

Postsynaptic neuron : Neuron on which neurotransmitters act.

Chemical synapse

i. *Definition* : Chemical synapses are the most common types of synapses present in human body. The neurons communicate via chemical transmitter i.e. neurotransmitters such as acetylecholine, serotonin.

   This chemical mediators binds to receptors on the surface of the post synaptic cell, and this triggers events that open or close channels in the membrane of the post synaptic cells.

   The chemical synapses transmit signals in one way direction i.e. unidirectional.

ii. *Morphology of a chemical synapse* : (same as the funtional anatomy of a synapse).

Electrical synapses :

i. *Definition* : In electrical synapses, the membranes of the presynaptic and postsynaptic neurons come close together, and gap junctions form between the cells.

   Like the intercellular junctions in other tissues, these junctions form low-resistance bridges through which ions pass with relative ease. There is electrical coupling, for example, between some of the neurons in the lateral vestibular nucleus.

   The electrical synapses transmit signals in two way direction i.e. bidirectional.

Q. 02. **Briefly describe the summation of synaptic transmission.**

Ans. *Summation of synaptic transmisssion* :

i. *Definition* : In synaptic transmission multiple excitatory or inhibitory stimuli can be summated and thus produce EPSP or IPSP respectively.

ii. Types : Summation is of two types spatial summation and temporal summation-
   a. *Spatial suntmation* : The effects of simultaneous discharge of many synaptic knobs over a wide area of the postsynaptic terminal can summate i.e. activity in one synaptic knob is said to facilitate activity in another to approach the firing level and produce FPSPs or IPSPs. This is called spatial summation.
   b. *Temporal summation* : The effect of successive discharge of a presynaptic terminal on the postsynaptic membrane can also summate and produce EPSPs or IPSPs. This is called temporal summation.

Q. 02. **Briefly describe the synaptic delay.**

Ans. *Synaptic delay* :

i. *Definition* : A certain amount of time is consumed in the transmission of an action potential from a presynaptic neuron to a postsynaptic neuron. This is called synaptic delay.
ii. *Duration* : About 0.5 millisecond.
iii. *Causes* :
   a. Delay in the release of neurotransmitters.
   b. Passing of neurotransmitters through the synaptic cleft.
   c. Delay in the combination of neurotransmitter with post synaptic receptors.
   d. Delay in the set up of action potential.
iv. *Importance* : To determine the synaptic pathway whether it is monosynaptic or polysynaptic. Minimum delay across one synapse is 0.5 ms. Delay > 0.5 ms indicates numbers of series of neurons in the circuits :
   * In monosynaptic pathway : delay 0.5 milli second.
   * In polysynaptic pathways : delay will be> 0.5 milli second.

Q. 02. **Briefly describe the synaptic inhibition.**

Ans. *Synaptic inhibition* :

i. *Definition* : Inhibition of synapses.
ii. Types : Synaptic inhibition may be of following types :
   a. *Direct inhibition* : Inhibition during the course of an IPSP is direct inhibition.
   b. *Indirect inhibition* : Inhibition during refractory period is called indirect inhibition.
   c. *Presynaptic inhibition* : The inhibition caused by *presynaptic synapse (axoaxonal)* that lies on the terminal nerve fibrils before they themselves terminate on the following neuron i.e. postsynaptic neuron.

      Mechanisms : Activation of these synapse on the presynaptic terminal causes :
      * Increase Cl^- influx in the presynaptic terminal and thus reduces amplitude of the action potential in the presynaptic terminal that causes reduced Ca^{++} influx

in the presynaptic terminal for neurotrailsmitter release.

* Activation of these synapse also cause voltage gated K^+ channels to open and the resulting K^+ efflux also decreases Ca^{++} influx.
* Activation of these synapses cause direct inhibition of transmitter release indepen- dent of Ca^{++} influx into the excitatory ending.

d. *Postsynaptic inhibition* : The inhibitions caused by inhibitory interneuron that make synapse with presynaptic terminal and ends on postsynaptic membrane and secrete inhibitory transmitter i.e glycin.

Excitatory post synaptic potential (EPSP) : When an excitatory impulse excites a motor neuron, depolarization of the membrane occurs. This is called EPSP. When the stimulus is stronger, EPSP reaches the threshold level and the nerve impulse is set up.

Cause : The excitatory impulse increases the Na^+ permeability to the post synaptic membrane and causes EPSP.

Inhibitory post synaptic Potential (IPSP) : When a motor neuron receives an inhibitory impulse, hyperpolarization of the cell membrane occurs. This is called IPSP. The hyperpolarization exerts an inhibitory effect on EPSP and depolarization of the cell membrane and causes inhibition in setting up the nerve impulse.

Cause : IPSP is due to the increased permeability of post synaptic membrane to K^+ & CI^- instead of Na^+.

Neurotransmiter

These are highly active chemical agents releases at the nerve ending and transmits impulses from nerve to nerve or from nerve to effector tissue.

Some neurotransmitter :

1. *Excitatory*
   a. Acctylcholine
   b. Adrenaline
   c. Noradrenaline
   d. Glutamate.
2. *Inhibitory*
   a. Dopamine
   b. Glycin
   c. Taurine
   d. Alanine.
   e. GABA
   f. Serotonin.
3. *Both excitatory and inhibitory*
   a. 5-HT (hydroxytryptamine)
   b. Histamine
   c. Prostaglandine.
   d. Nor-epinephrine.

(Ref. Guyton & Hall 11th edition; page 562)

Small molecule, rapidly acting transmitters

Class I : *Acetylecholile*

Class II : *The amines* :
Norepinephrine
Epinephrine
Dopamine
Serotonin
Histamine.

Class III : *Amino acids* :
Gama Aminobutyric acid (GABA)
Glutamate
Asparate.

Class IV : Nitric Oxide (NO).

(Ref. Guyton & Hall 11th edition; page 562)

Neuropeptides, slowly acting transmitters

a. *Hypothalamic releasing hormones :*
Thyrotropin releasing hormone
Luteinizing hormone-releasing hormone
Somatostatin (growth hormone inhibitory factor).

b. *Pituitary peptides :*
ACTH
Beta Endorphin
Alpha melanocyte-stimulating hormone
Prolactin
Luteinizing hormone
Thyrotropin
Growth hormone
Vasopressin
Oxytocin.

c. *Peptides that acts on gut and brain :*
Leucine enkephalin
Methionine enkephalin
Substance P
Gastrin
Cholecystokinin
Vasoactive intestinal polypeptide (VIP)
Neurotensin
Insulin
Glucagon.

d. *From other tissues :*
Angiotensin II
Bradykinin
Carnosine

Ref. Guyton & Hall 11th edition.

Sleep peptides
Calcitonin.

(Ref. Guyton & Hall 11th edition; page 563)

Site of acetylcholine secretion : *Acetylcholine is secreted by* :

i. The preganglionic neuron of autonomic nervous system.
ii. The post ganglionic neuron of parasympathetic system.
iii. The motor neurons innervate the skeletal muscle.
iv. The postganglionic neuron of sympathetic system that innervate the sweat and sebaceous gland.
v. Also from brain, cortex and basal ganglia.

Site of Adrenaline secretion : *Adrenaline is secreted by-*

i. The post ganglionic neuron of sympathetic system, except those innervate the sweat and sebaceous gland.
ii. The adrenal mdulla.

Q. 00. **Briefly discuss the sites of synthesis of the neurotransmitters.**

Ans. Sites of synthesis of neurotransmitters :

a. *Cytosol of the presynaptic terminal* : Principal neurotransmitters (small molecular types of transmitters) are synthesized in the cytosol of the presynaptic terminal.
b. *Ribosome in the neuronal cell body* : Neuro- peptides.
c. *Cell organelles* : That take part in the synthesis of neurotransmitter are :
   * Nisslgranules
   * Golgi complex
   * Mitochondria.

Q. 00. **Briefly discuss the storage of the neuro-transmitters.**

Ans. *Storage of neurotransmitters* : Neurotrans- mitters are stored in the synaptic vesicles. The neurotransmitter vesicles are distributed throughout the presynaptic nerve terminal. There are three kinds of synaptic vesicles :

a. *Small and clear synaptic vesicles* : Contain acetylcholine, GABA and glycin.
b. *Small with a dense vesicle* : Contain catecholamines.
c. *Large vesicles with a dense core* : Contain neuropeptides.

Q. 00. **Briefly discuss the mechanism of neuro-transmitter release.**

Ans. *Mechanism of neurotransmitter release* : Neuro-transmitter vesicles discharge their contents into the synaptic cleft by the process of exocytosis which requires :

a. Ca^{++} ions :
b. Energy
c. Docking proteins : synaptobrevin and syntaxin.

Ca^{++} ions are the key to synaptic vesicle fusion and discharge. The active zone (area of membrane thickening) of the presynaptic terminal contains rows of Ca^{++} channels. The quantity of transmitter release is directly proportional to the number of Ca^{++} influx.

Thus the processes of release are :

a. Action potential in the presynaptic nerve terminal opens voltage gated Ca^{++} channels and thus Ca^{++} influx occurs in the presynaptic terminal.
b. Ca^{++} influx triggers the release of neurotransmitter by binding and fusion of synaptic vesicle with the presynaptic memhrane. Protein that interact to produce synaptic vesicle docking and fusion with the presynaptic membrane are synaptobrevin in synaptic vesicle and syntaxin in the presynaptic membrane.
c. The area of fusion breaks down and transmitters are released into the synaptic cleft.

Small clear vesicles and the small dense core vesicles recycle in the ending.

Large dense core vesicles are autolysed and are not reused.

The Ca^{++} concentration is restored to the resting level by rapid sequestration and removal from the cell, primarily by a Ca^{++}-Na^{+} antiport.

Q. 00. **Briefly discuss the fate of neurotransmitter.**

Ans. Fate of neurotransmitter : After a transmitter is released at a nerve ending, it is either destroyed or removed from the synaptic cleft. The functional significance of this is that it prevents an undesirable sustained effect of neurotransmitter on the postsynap- tic neuron.

This removal is achieved by-

a. By *diffusion* of the transmitter out of the cleft into the surrounding fluids.
b. By enzymatic destruction within the cleft itself.

$$\text{Acetylcholine} \xrightarrow{\textit{Cholinesterase}} \text{Acetate} + \text{choline}$$

Catecholamines (adrenaline, noradrenaline) by monoamine oxidase (MAO).

c. By reuptake of transmitter into the presynaptic terminal by active transport.

Q. 00. **What is neuromodulators** (co-transmitter)?

i. *Definition* : Neuromodulators or neuropeptides are the chemical substances that can co-exist with the principal transmitter at a single synapse i.e in separate synaptic vesicle or in the same vesicle and are ejected from the presynaptic terminal into the synaptic cleft having the capability of modulating and modifying the activity of the principal transmitter.

ii. *Examples* :
   a. Substance - P
   b. Neurotensin
   c. Bradykinin
   d. Adenosine
   e. Neuropeptide-Y.

Q. 03. **Compare the principle neurotransmitters and neuromodulators.**

Ans. Comparison between the principle neurotrans- mitters and neuromodulators :

Points	*Principle neurotransmitter*	*Neuromodulator*
Action	Rapid excitation or inhibition of post synaptic membrane activity	Modulation and modification of principal neurotrans-mitter.
Site of action	Directly acts on postsynaptic membrane	Have no direct action on postsynaptic membrane
Duration	Short	Prolonged
Sites of synthesis	Cytosol of presynaptic nerve	In the soma by ribosomes
Location	Main sensory and motor system	Systems that control homeostasis
Size	Small molecule	Large molecule
Amount released	Large quantity	Small quantity
Potency	Less	> 1000 time potent
Receptor	Ion channels	G protein coupled receptor
Types of action.	Acute response	Delayed response

Neuromuscular junction

i. *Definition* : The junction between muscle fibre and motor nerve ending is called neuromuscular junction.

ii. *Description of a neuromuscular junction* :

a. *Axon terminal or end feet :* At the junction the nerve fibre losses myelin sheath and ends by dividing into many branches called axon terminal or end feet.
Content of axon terminals : It contain mito- chondria which provides energy and vesicles which contain neurotransmitter.

b. *Synaptic gutter* : The axon terminal lie within the synaptic gutter which is formed by the invagination of *sarcolema into sarcoplasm.*

c. *Synaptic cleft* : The gap between sarcolema and end feet is called synaptic cleft which is filled with ECF.

d. *Motor end plate* : The thickening portion of muscle fibre adjacent to end feet is called motor end plate.

Neuromuscular transmission

Sequence of event of neuromuscular transmission are given below :

i. Arrival of motor impulse at motor nerve terminal.

ii. Enter of Ca^{++} into the vesicles of end feet.

iii. Release of acetylcholine from prejunctional nerve terminal vesicle.

iv. Diffusion of acetylcholine across the synaptic cleft.

v. Acetylcholine binds to the receptor of motor end plate and increases the permeability of Na^{+} and production of local end plate potential (depolarization).

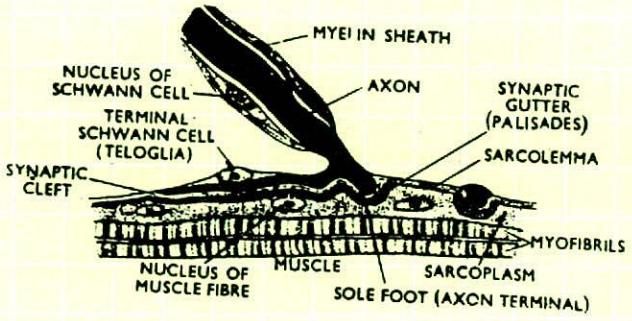


Fig. 16-6. Neuromuscular junction.

vi. When the end plate potential reaches the certain critical magnitude then the muscular membrane will be depolarized and set up a propagated action potential in muscle causes to the spike potential.

vii. Then the spike potential preceed and mechanical tension of muscle takes place.

(Ref. Wright's 13th page-257)

Receptor

Definition : Receptors are the specialised tissue that can be stimulated by any changes of both external or internal environment.

Classification of sensory receptors

I. ***Mechanoreceptors*** :

Skin tactile sensibilities
(epidermis and dermis)
Free nerve endings
Expanded tip endings
Merkel's discs
Plus several other variants
Spray endings
Ruffini's endings
Encapsulated endings
Meissner's corpuscles
Krause's corpuscles
Hair end organs

Deep tissue sensibilities
- Free nerve endings
- Expanded tip endings
- Spray endings
  - Ruffini's endings
- Encapsulated endings
  - Pacinian corpuscles
  - Plus a few other variants
- Muscle endings
  - Muscle spindles
  - Golgi tendon receptors
- Hearing
  - Sound receptors of cochlea
- Equilibrium
  - Vestibular receptors
- Arterial pressure
  - Baroreceptors of carotid sinuses and aorta

II. ***Thermoreceptors***
- Cold : Cold receptors
- Warmth : Warm receptors

III. ***Nociceptors***
- Pain : Free nerve endings

IV. ***Electromagnetic receptors***
- Vision
  - Rods
  - Cones

V. ***Chemoreceptors***
- Taste : Receptors of taste buds
- Smell : Receptors of olfactory epitheliurn
- Arterial oxygen
  - Receptors of aortic and carotid bodies
- Osmolality
  - Probably neurons in or near supraoptic nuclei
- Blood CO_2
  - Receptors in or on surface of medulla and in aortic and carotid bodies
- Blood glucose, amino acids, fatty acids
  - Receptors in hypothalamus.

(Ref. Guyton & Hall10th Edition; page-529)

Classification of receptor *(In Short)* : It is difficult to classify receptors. Different in structure, location & function they are of various types. Few of them are postullated below :

A. ***According to sensitivity to a particular form of energy :***

1. *Mechanoreceptor :* Which concern with mechanical deformation of receptor.
   Example : Baroreceptors of carotid and aortic sinuses.
2. *Thermoreceptor :* Which detect the change of temperature.
   Example : End bulb of Krause, End organ of Ruffini.
3. *Naciceptor :* Which detect the damage of tissue.
   Example : Free nerve ending (pain receptor).
4. *Electromagnatic receptor :* Which detect light on the retina of the eye.
   Example : Rod, cone.
5. *Chemoreceptor :* Detect any chemical change of the body.
   Example : Carotid and aortic bodies.

(Ref. Guyton & Hall 11th edition; page 529)

B. ***Accroding to distribution*** :

1. *Exteroceptor :* These are distributed to body surface and are stimulated by changes in external environment.
2. *Proprioceptor :* These are distributed to the muscle, tendons, joints etc.
3. *Interoceptor :* These are distributed to the viscera, blood vessels etc.

(Ref. Wright's 13th page-285)

C. ***Broadly, receptors are classified into*** :

1. *Exteroceptors :* Those which collect information from out side of the body. It is subdivided into-
   a. Cutaneous receptors :
      Example : Receptor for pain, touch, temperature, cold, pressure, tickling, itches.
   b. Tele receptors (Distance receptor) :
      Example : Receptor for vision, audition, olfaction.
2. *Interoceptors :* Those which collect information from inside of the body. These are-
   a. Proprioceptors : These are carrying information from muscles, tendons, joints etc.
   b. Visceroceptors :
      Example : Chemoreceptors, pain, baroreceptors, stretch receptors, osmoreceptors etc.

Properties of receptor

1. *Excitability :* Receptors are excited by stimulus of electrical, mechanical, thermal or chemical stimuli.
2. *Specificity :* Specific receptor is only stimulated by specific stimulus.
3. *Adaptaion :* When a maintained and constant stimulation is applied to receptor the frequency of discharge from that of receptor will gradually decline. This is called adaptation.
4. *Intensity discrimination :* Several receptors acting

Some receptors with their function & location

Receptor	*Function/sensation*	*Location*
Cutaneous receptor :		
1. Free nerve ending	Pain (mainly), touch, pressure.	Mainly dermis, cornea, also in muscle tendon, vessels etc.
2. Meissner's corpuscles	Touch (tactile localisation)	Superficial aspect of the dermis of hand, foot, nipple, lips, tip of the tongue & in the dermal papillae.
3. Markel's disc	Light touch.	Highly sensative areas (lips, fingers, genitalia).
4. End bulbs of Krause	Cold.	Dermis of skin (Conjunctiva, papillae of skin, lip, tonuge, genitalia), epineurium of nerve.
5. End organ of Ruffini	Heat.	Dermis of skin.
6. Pacinian corpuscles (Largest end organ)	Pressure.	Subcutaneous tissue, tendons of muscles, capsular ligament of joints, in the wall of the blood vessels, mesen teries & periosteum.
7. Golgi-Mazzoni bodies	Pressure.	Subcutaneous tissue, tendons of muscles, capsular ligament of joints, in the wall of the blood vessels, mesen teries & periosteum.
Proprioceptors *(Muscular receptor) :*		
1. Muscle spindle	Carries kinesthetic sensation. Maintains position, Maintains muscle tone, Mediate protective reflexes when muscle vigorously contract.	Between the muscle fibre
2. Tendon end organ of Golgi	Carries kinesthetic impulse. Send inhibitory impulse to inhibit the hypercontraction of muscle & tendon.	Tendons near the junction with muscle
3. Joint receptors a. Pacinian b. Golgi type I & II c. Ruffini's end organ.	Maintains the position & Movement of joint	Ligaments & Capsule of joint.

conjointly and help us to give information about the shape, size, texture and weight of an object.

5. *Doctrine of specific nerve energies :* The sensation evoke by any stimulation, the impulse generated in the receptor depends upon specific part of the brain which is ultimately activated.
6. *Projection :* When any part of the sensory pathway is stimulated, conscious sensation is referred to the location of receptor, this is called law of projection.

Q. 02. **Give the list of proprioceptors.**

Ans. Proprioceptors :

i. Muscle spindle
ii. Tendon end organ of Golgi
iii. Joint receptors :

a. Pacinian
b. Golgi type I & II
c. Ruffini's end organ.

Q. 02. **Give the list of cutaneous receptors.**

Ans. Cutenious receptors i.e. skin tactile sensibilities (epidermis and dermis) are :

a. Free nerve ending
b. Meissner's corpuscles
c. Markel's disc
d. End bulbs of Krause
e. End organ of Ruffini
f. Hair end organs.

(Ref. Guyton & Hall 11th edition)

Q. 05. **Discuss the location and functions of the cutaneous receptors.**

Ans. *Cutaneous receptors* :

Receptor	*Location*	*Function*
Free nerve endin	Mainly dermis, cornea, also in muscle, tendon vessels etc	Pain (mainly), touch and pressure.
Meissner's corpuscles	Superficial aspect of the dermis of hand, foot, nipple, lips, tip of the tongue & in the dermal papillae.	Touch (tactile localisation)
Markel's disc	Highly sensative areas i.e lips, fingers, genitalia.	Light touch
End bulbs of Krause	Dermis of skin (Conjunc tiva, papillae of skin, lip, tonuge, genitalia), epineurium of nerve.	Cold sensation
End organ of Ruffini.	Dermis of skin	Heat

Sensation

It is the feelings evoked by stimulus.

Sensory unit : The area of skin supplied by single nerve fibre is called sensory unit.

Modality of sensation

Sensory receptors are specialized to respond to one particular form of sensation or energy. Thus each main type of sensation that can be experienced is called a *modality of sensation.* Sensory modalities can be divided into two groups :

i. ***Conscious sensations*** :
   a. Pain
   b. Temperature : heat or cold
   c. Touch
   d. Pressure
   e. Joint position and movement
   f. Vision
   g. Hearing
   h. Smell
   i. Taste.

ii. ***Unconscious sensations*** :
   a. Arterial PO_2
   b. pH of CSF
   c. Arterial blood pressure
   d. Central venous pressure
   e. Muscle tension and length
   f. Osmotic pressure of plasma
   g. Arteriovenous blood glucose difference.

(Ref. Guyton & Hall 11th edition; page 572)

Low of specific nerve energies

The specificity of nerve fibre for transmitting only one modalities of sensation is called the low of specific nerve energies. Example-Pain is transmitted by a specific nerve fibre, temperature by another types of fibre etc.

End organ

These are specially organized body at the end of either a motor nerve or at the peripheral end of a sensory nerve, which transmit impulses to the efector organ or receive a particular stimuli from the periphery.

Receptor potential

i. *Definition* : Whatever the type of stimulus that excites the receptor, its immediate effect is to change the potential across the receptor membrane. This change in potential is called *receptor potential.*
   When the receptor potential rises above the threshold for eliciting action potentials in the nerve fiber attached to the receptor, then action potentials begin to appear.

ii. *Characteristics* :
   a. Non-propagated
   b. Have no refractory perroid
   c. Graded.
   d. Does not follow all-or- law.

(Ref. Guyton & Hall 11th edition; page 573-574)

Q. 02. **Distiguish between the receptor potentials and action potentia.**

Ans. Differences between the receptor potentials and action potential :

Action potential	*Receptor potential*
a. Propagated	a. Non-propagated
b. Have refractory peroid.	b. Have no refractory perroid

Action potential	*Receptor potential*
c. Non-graded	c. Graded.
d. Follows all -or-none law	d. Does not follow all-or-none law.

Q. 02. **What is adaption? Compare rapidly and slowly adapting receptors.**

Ans. *Adaptaion* :

i. *Definition* : When a maintained and constant stimulation is applied to receptor the frequency of discharge from that of receptor will gradually decline. This is called adaptation.

Comparison between rapidly and slowly adapting receptors :

Rapidly adapting receptors	*Slowly adapting receptors*
a. Receptors adapt rapidly	a. Recetors adapt slowly and incompletely.
b. Example : touch receptors	b. Example : Carotid sinus, muscle spindles, free nerve ending, end bulb of krause etc.
c. Rapidly adapting receptors detect change in stimulus strength.	c. Slowly adapting receptors detect continous stimulus strength.
d. Also called phasic recptor	d. Also called tonic receptor.

Reflex

Definition : Reflex is the involuntary motor response due to any type of sensory stimulation which is mediated through the CNS.

Importances of examination of reflexes

i. Skeletal muscles receives a segmental innervation. Most of these muscles are innervated by more than one spinal nerve and, therefore, by the same number of segments of the spinal cord. Thus, to paralyze a muscles completely it would be necessary to section several spinal nerves or destroy several segments of the spinal cord.

ii. To learn the segmental innervation of all the muscles of the body is an impossible task. Nevertheless, the segmental innervation of the muscles should be known, because it is possible to test them by eliciting simple muscle reflexes in the patient.

Classification of reflex

Reflex are classified principally of two types :

a. *Uncondition or inborn* : These are inheritent, fixed and cannot altered normally. *Example* : Knee jerk.

It is further classified into three types :

i. *Superficial reflex :* Here the stimuli are received by the skin or mucous membrane. *Example* : Plantar, abdominal and corneal reflex.

ii. *Deep reflex :* Here the stimuli are applied on the tendons. *Example* : Knee jerk, Ankle jerk, Biceps jerk etc.

iii. *Visceral reflex :* These are obtained from deep structures such as viscera. Ex. Micturation, defecation, vomitting reflex.

b. *Condition reflex* : Condition reflex is a reflex response to a stimulus which never produce previously but has been acquired by pairing the said stimulus repeatedly with one uncondition stimulus which normally produces the response. Example- Pavlov's experiment.

Properties of reflex

1. *Localization :* If a specific stimulation is given to a particular locus, then specific response will be evoked.
2. *Delay :* It is the interval in between the time of giving stimulation and getting response. It is about 18-25 milisec.
3. *Summation :* If a subminimal stimulus is applied to a receptor or a sensory neuron, the motorneuron will not discharge impulse but application of a number of subminimal stimuli will evoke reflex action, called summation.

   Cause : Application of a subminimal stimulus will produce insufficient EPSP where as a number of stimuli evoke sufficient EPSP-will cause reflex action.

   Types : It is of two types :

   a. *Spatial summation :* If two afferent nerve stimulated separately, action will not produce. But if they are stimulated repeatedly, reflex action will evoke.

   b. *Temporal summation :* Application of a number of subminimal stimuli on the same nerve will evoke reflex action but a individual stimulus will not produce reflex action.

4. *Occlution :* When a reflex action is produced by the simultaneous stimulation of two afferent nerve, the amount of tension in the muscle is less than the sum total tension set up in the same muscle by stimulating the two nerve separately, This is due to the some neuron which are common for both nerve.
5. *Subliminal fringe :* It is opposite the occlution. The total tension in the muscle due to separate stimulation of two nerve is less than the tension obtained with simultaneous stimulation. Here stimulus is sub-threshold.

   Explanation : During separate stimulation the impulse become adequate for some neurons and inadequate for others. But during simultaneous stimulation the impulse summated and become stronger.

6. *Facilation :* If a reflex elicited repeatedly at proper intervals,

Methods of eliciting, center and response of some superficial and deep reflex :

Name	*Method of eliciting*	*Response*	*Centre*
Superficial reflex			
1. Plantar	Scratching of the skin of sole.	Normally plantar flexion of great toe in adult but incase of infant it becomes dorsiflexion of great toe with fanning of other toes.	Lumber 5 to sacral 2 probably S_1.
2. Anal	Scratching of the skin of the perineum.	Contraction of external anal sphincter.	S_4 & S_5
3. Gluteal	Scratching of the skin of buttock.	Contraction of the gluteal muscles.	L_4, L_5 and upper sacral segments.
4. Pupillary	Fall of light on eye.	Contraction of pupil.	3rd cranial nerve nuclei.
5. Abdominal	Stroking abdominal wall below costal margin	Contraction of abdominal muscles	T_7 - T_{12}
6. Cremesteric	Stroking skin at upper and inner part of thigh	Upward movement of testicle	L_1 - L_2.
Deep reflex or tendon reflex :			
1. *Knee jerk*	Tapping of patellar tendon on semiflexed knee.	Forward jerking of leg due to contraction of the quadriceps femoris muscle.	L_2 to L_4
2. *Ankle jerk*	Tapping of tendo-calcaneous.	Plantar flexion of foot due to contraction of the gastrocnemius	L_5 to S_2
3. Supinator jerk	Tapping on the styloid process of the radius	Flexion and supination of the forearm	C_5 - C_6
4. Biceps jerk	Tapping of biceps tendon.	Flexion of forearm.	C_5 & C_6
5. *Triceps jerk*	Tapping of triceps tendon.	Extension of forearm due to contraction of triceps	C_6 to C_8

the response become progressively higher for the Ist few occasions and the reflex delay decreases.

7. *Reciprocal innervation :* If an afferent nerve is stimulated the protogonist contracts and the antagonist relaxes. This phenomenon is called reciprocal innervation.
8. *Fatigue :* If the reflex is excited repeatedly the response become gradually weaken and ultimately ceases. It is called fatigue.
9. *Recruitment :* If we stimulate a neuron reflexly, the tension develope gradually to the pick. As because after repeated stimulation of the afferent nerve, more and more internuntial neurons are activated; then they activates motor nerve. This phenomenon is called recruitment, as because more and more neurons are recruited.
10. *After discharge :* After reflex contraction if the stimulus is discontinued, the muscle does not completely relaxed at once but it relax gradually. As because the motor neuron stop discharge successivly.

Reflex arc

Definition : Reflex arc is the complete pathway of reflex action.

It consist of the following parts :

1. Receptor
2. Afferent nerve
3. Center
4. Synapse
5. Efferent nerve
6. Effector organ.

Classifications of reflex arc :

1. *Monosynaptic reflex arc :* Has two neuron or only one synapse.
   Example : Stretch reflex.
2. *Disynaptic reflex arc :* Has two synapse or three neurons.
   Example : Extension and crossed extension reflex.
3. *Polysynaptic reflex arc :* Here the synapse is more than two

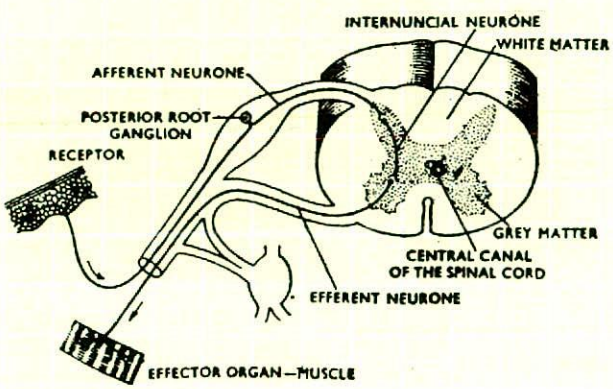


Fig. 16-7. *Reflex arc*

and more than one internuncial neuron exists.

Example : Withdrawl reflex.

Knee jerk

Definition : Knee jerk is one of the deep reflex. Tapping on patellar tendon in semiflex knee causes contraction of quadriceps muscle and forward jerking of leg is called knee jerk

1. *Stimuli* : Sharp tapping on patellar tendon of semiflexed knee.
2. *Response* : Forward jerking of leg.
3. *Centre* : L_2 to L_4 of spinal cord.
4. *Pathway of knee jerk* : Tapping on patellar tendon → Stretched of quadriceps muscle spindle → Stimulation of afferent nerve → Afferent impulse to the center of spinal

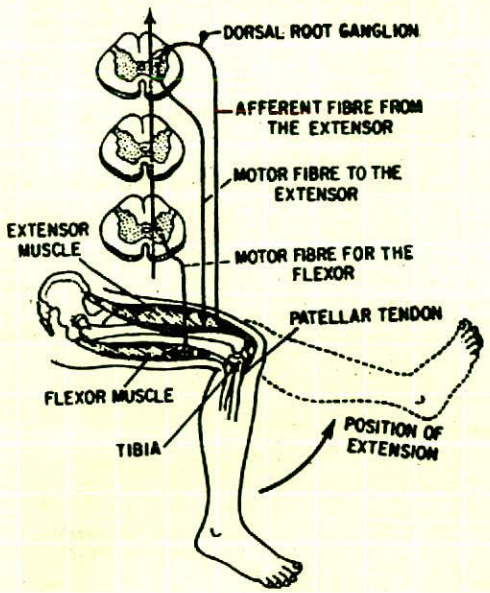


Fig. 16-8. *Knee jerk.*

cord via dorsal root ganglion → Synapse with alpha motor neuron → Motor impulse → Motor nerve to the quadriceps muscle → Contraction of quadriceps and relaxation of flexor muscle → Causes jerking forward of leg.

5. *Importance of knee jerk* :
   1. It is abolishes in lower motor neuron paralysis.
   2. Exaggerated in upper motor neuron paralysis.
   3. Pendular in cerebellar lession.

Stretch Reflex

i. *Definition* : Whenever a muscle is stretched, excitation of the spindles cause reflex contraction of the muscle and this is called stretch reflex.

ii. *Example* : i.e monosynaptic reflexes-
   a. *Knee jerk* : Forward jerking of leg due to reflex contraction of the quadriceps femoris muscle.
   b. *Ankle jerk* : Plantar flexion of foot due to reflex contraction of the gastrocnemius muscle.
   c. *Tricep jerk* : Extension of forearm due to reflex contraction of triceps etc.

iii. *Types* : It can be divided into two separate components called static reflex and a dynamic reflex.
   a. *The dynamic stretch reflex :* When a muscle is suddenly stretched, a strong signal is transmitted to the spinal cord, and this causes an instantaneous, very strong reflex contraction of the same muscle from which the signal originated- this is called dynamic stretch reflex. Thus, the reflex functions to oppose sudden changes in the length of the muscle, because the muscle contraction opposes the stretch.
   b. *The static reflex :* The dynamic stretch reflex is over within a fraction of a second after the muscle has been stretched to its new length but then a much weaker reflex continues for a prolonged period of time thereafter which- is called static reflex. The importance of this reflex is that it continues to cause muscle contraction as long as the muscle is maintained at an excessive length. The muscle contraction inturn opposes the force that is causing the excess length.

iv. *Importance* : The importance of the stretch reflex is that it continues to cause muscle contraction as long as the muscle is maintained at an excessive length. The muscle contraction inturn opposes the force that is causing the excess length.

(Ref. Guyton & Hall 11th edition)

Negative stretch reflex : If a muscle is already taut, any sudden release of the load on the muscle that allows it to shorten will elicit both dynamic and static reflex muscle inhibition rather than reflex excitation, this is called negative stretch reflex.

(Ref. Guyton & Hall 11th edition)

Withdrawal reflex : Any type of cutaneous sensory stimulus on a limb to cause the flexor mucles of the limb contract, thereby withdrawing the limb from the stimulus. This is called the withdrawal reflex or flexor reflex.

(Ref. Guyton & Hall 11th edition)

Crossed extensor reflex : Approximately 0.2 to 0.5 second after a stimulus elicits a flexor reflex in one limb, the opposite limb begins to extend. This is called the crossed extensor reflex.

(Ref. Guyton & Hall 11th edition)

Tracts

Tracts may be defined as a bundle of nerve fibres carring one or a group of motor or sensory impulses to and from the brain.

Types :

Tracts are of two types-

a. Ascending tracts or sensory tract
b. Descending tracts or motor tract

Tracts of spinal cord

i. ***Ascending tract***
   a. *Posterior funiculus :*
      1. Tract of Gall
      2. Tract of Burdach
      3. Inter segmental tract.
   b. *Anterior funiculus :*
      1. Anterior spinothalamic tract
   c. *Lateral funiculus :*
      1. Lateral spinothalamic
      2. Dorsal spino cerebellar
      3. Ventral spinocerebellar
      4. Spino-tectal
      5. Spino-olivary
      6. Spino-reticular
      7. Spino-vestibular.

ii. ***Descending tract***
   a. *Pyramidal tract :*
      1. Lateral corticospinal or crossed pyramidal tract.
      2. Anterior corticospinal or uncrossed pyramidal tract.
      3. Uncrossed lateral corticospinal tract.
   b. *Extrapyramidal tract :*
      1. Rubrospinal tract.
      2. Tectospinal tract.
      3. Olivo-spinal tract.
      4. Recticulo-spinal tract.
      5. Vestibulo-spinal tract.
   c. *Cortico-bulbar tract.*

Tract of gall & tract of Burdach

Extension : These tract lies in the posterior funsiculus. Tract of Gall extend through out the cord. Below the mid thoracic level, it occupies the whole breadth of posterior funiculus but above this it lies medial to the tract of Burdach which extend only above the mid thoracic level.

Origin : These tracts are made up of axons of the bipolar cells of the dorsal root ganglia. Tract of Gall receiving afferent fibre from lower half and Burdach receiving from the upper half of the body.

Course :

a. *1st order neuron :* These are the axon of the dorsal root ganglia. After entering into the spinal cord the fibres end in the following ways :
   1. Majority of fibres ascend and terminate in the nucleus gracil (GALL) & nucleus cuneatus (Burdach).
   2. Some fibres make reflex connection at different segment of spinal cord.
   3. Some fibres descend and make the comma tract of Schultze.

b. *2nd order neuron :* These are the axons of the cells of gracils and cuneatus nucleus and divide into two group :
   i. External arcuate
   ii. Internal arcuate fibre.

   External arcuate fibres are redivided into dorsal and ventral groups. Dorsal group goes to the same side cerebellum but ventral group goes to opposite cerebellum. The internal arcuate fibre crosses and goes to opposite side enters the

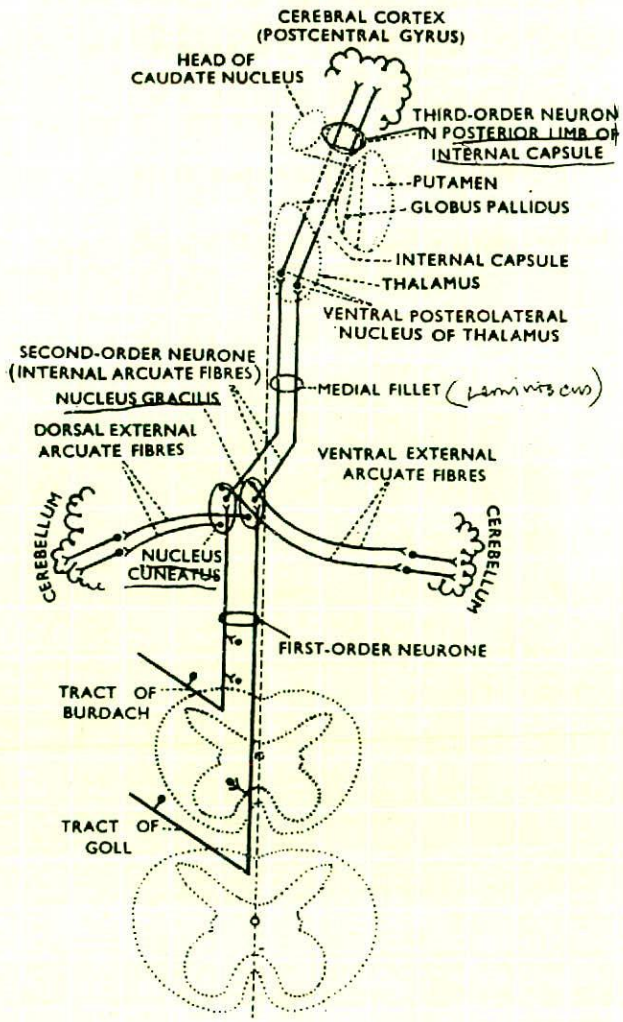


Fig 16-9. *Diagramatic reprentation of tracts of Gall and tract of Burdach.*

medial lemniscus and terminate into the ventral posterolateral nucleus of the thalamus.

c. *3rd order neuron :* Passes through the posterior limb of internal capsule and end into the somatostatic area or post central gyrus of cerebral cortex.

Functions :

1. Carries kinesthetic sensation.
2. Carries fine touch sensation.
3. Carries tactile localization.
4. Carries tactile discrimination.
5. Carries sense of vibration.
6. Sensory pathway for superficial reflex.

Spinothalamic tact

1. Anterior spinothalamic tract.
2. Lateral spinothalamic tract.

Extension : From the spinal cord to the thalamus and take position into opposite anterior and lateral funiculus respectively.

Origin & course :

a. *1st. order neuron :* Formed by the axons of the cells of dorsal root ganglia in the spinal cord. These fibres ends in the posterior horn cell of same side.

b. *2nd order neuron :* These are the axons of the nucleus centrodorsalis of posterior horn, crosses the white comissure goes to the anterior and lateral funiculus of opposite side and ascend as anterior and lateral spinothalamic tract respectively and finally terminate into the ventrobasal nucleus of thalamus and 3rd order neuron arises.

c. *3rd order neuron :* These fibre terminate into the somatosensory area of cortex.

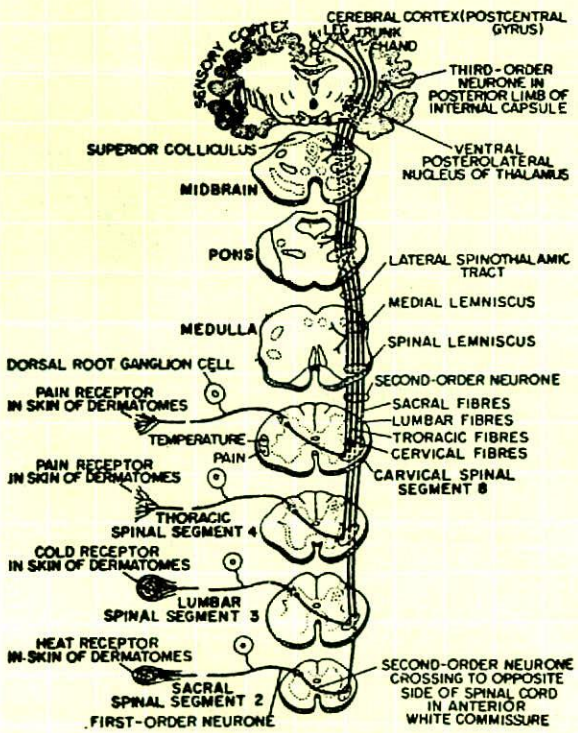


Fig. 16-10. *Spinothalalic tract*

Functions :

1. *Anterior spinothalamic :*
   a. Carries impulse of crude touch of opposite side.
   b. Carries pressure sensibility of opptsite side.
2. *Lateral spinothalamic :*
   a. Carries painful sensation of opposite half.
   b. Carries both hot and cold sensation of opposite side.
   c. Carries complex sensation (tickling & itching).

Cortico-spinal tract

Pyramidal system and extrapyramidal system

i. *Pyramidal system* : Because the fibers of the lateral corticospinal tract form the pyramids in the medulla, the corticospinal pathways have often been referred to as the *pyramidal system.*

ii. *Extrapyramidal system* : The rest of the descending brain stem and spinal pathways that do not pass through the pyramids and are concerned with postural control have been called the extrapyramidal system.

However, the ventral corticospinal pathway does not go through the pyramids, many pyramidal fibers are concerned with other functions, and the system that used to be called extrapyramidal is made up of many different pathways with multiple functions. Consequently, the terms pyramidal and extrapyramidal are misleading, and *it seems wise to drop them.*

Pathway of cortico-spinal tract : As because, in the medulla it passes through the pyramid; so, it is called pyramidal tract.

Origin : The fibres arise from the giant pyramidal cell of Betz of the precentral gyrus. At the cortex, the fibres remain as upside down position, that is toes fibre remain at the top, trunk fibres middle and head fibres in the below.

Course : From cortex the fibres passes through corona radiata then their course are given below-

1. *In the Internal capsule :* Passes through genu and anterior 2/3 of posterior limb of internal capsule.
2. *In the mid brain :* Passes through the middle 2/3 of the crus ceriberi.
3. *In the pons :* This tract occupies the ventral aspect passing through the pontine nuclei where this tract forms scattered bundle.
4. *In the medulla :* Occupies in the pyramid in the lower part of the medulla, majority fibres crosses the midline and some fibre remains in the same side.

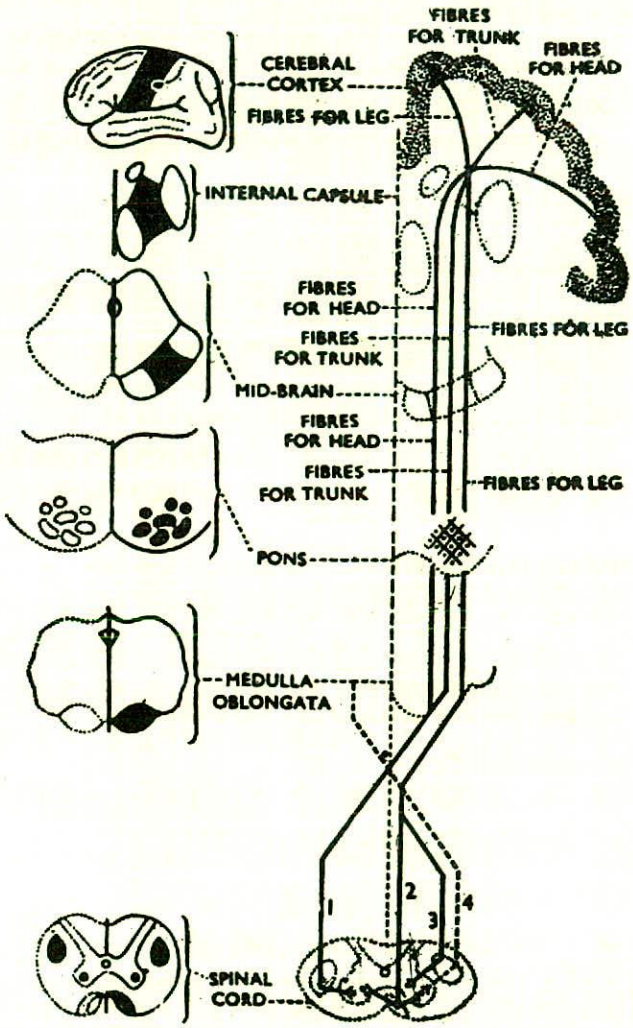


Fig. 16-11. *Cortico-spinal tract.*

5. *In the spinal cord :* The fibres terminate in the following way :
   i. The crossed fibre passes through lateral funiculus as lateral corticospinal tract and end in the anterior horn cells directly or through the internuncial neuron.
   ii. Some uncrossed fibre passes through anterior funiculus as anterior corticospinal tract and end opposite anterior horn cells and some end in the same side anterior horn cells directly or through internuncial neuron.
   iii. Some uncrossed fibres descend through lateral funiculus and end as lateral corticospinal tract.

Function pyramidal tract :

1. Convey motor impulses to the spinal cord for controlling voluntary fine movement of opposite side specially skillfull, and dancing type.
2. Constitute the pathway of superficial reflexes.

Functions of extra-pyramidal tract :

1. Movement of eye ball.
2. Responsible for tone, posture and equilibrium.
3. Responsible for complex movement of body and limbs.
4. It can transmit some voluntary impulse in case of pyramidal trct lesions.

Effect of pyramidal tract lesion :

a. *Changes in voluntary movement :*
   i. Disturbance in the voluntary movement of opposite arm and leg.
   ii. The discrete movements of fingers, walking, grasping, scratching etc can not perform properly.

Give the differece between pyramidal & extrapyramidal systems :

Points	*Pyramidal system*	*Extrapyramidal system*
1. Development	1. New motor system	1. Old motor system
2. Myelination	2. Starts at birth & is completed by 2nd or 3rd year.	2. Starts before birth
3. Onset of function	3. After completion of myelination.	3. From before birth.
4. Mode of discharge of impulse	4. Directly into Lower motor neuron in the anterior grey column in spinal cord.	4. Through already existing path by short interupted neurons. It is a poly synaptic multichannel cortical path way.
5. Nature of muscular activity	5. Non-postural, fine, isolated skill full movement of small muscles.	5. Gross postural movements affecting large muscle group.
6. Effect of damage	6. Flaccid paralysis. Incapacity & disability are more.	6. Spastic paralysis. Incapacity & disabilily are less.
7. Rate of conduction.	7. Slower	7. Faster.
8. Control in relation to body part.	8. Upper limb shows more pyramidal control.	8. Lower limb shows more extrapyramidal control.
9. Completion of work.	9. It finalizes the work	9. It concerned with tone, posture & equilibrium & setting up the platform for the work of pyramidal tract.

b. *Muscle tone :* Increases due to release phenomenon.

c. *Reflexes :*
   1. Superficial reflexes abolishd.
   2. Deep reflexes are exaggerated.
   3. Babinsk's sign positive.
   4. Knee and ankle clonus present.

Upper and lower motor neurons

In addition, the motor system has often been divided into upper and lower motor neurons.

i. *Upper motor neurons* : The neurons in the brain and spinal cord that activate the motor neurons.

   Effect of lesions :
   a. Spastic paralysis
   b. Hyperactive stretch reflexes
   c. Absence of muscle atrophy.

ii. *Lower motor neurons* : The spinal and cranial motor neurons that directly innervate the muscles.

   Effect of lesions :
   a. Flaccid paralysis
   b. Muscular atrophy
   c. Absence of reflex responses.

However, there are three types of *upper motor neurons* to consider. Lesions in many of the posture-regulating pathways cause spastic paralysis, but lesions limited to the *corticospinal* and *corticobulbar tracts* produce *weakness* (*paresis*) rather than paralysis, and the affected musculature is generally hypotonic. Cerebellar lesions produce incoordination. The unmodified term upper motor neuron is therefore *confusing*.

(Ref. Ganong 21th edition; page-203)

Q. Give the differece between upper motor lesion and lower motor lesion.

Upper motor lesion :	*Lower motor lesion*
1. Paralized muscles are rigid due to increase muscle tone.	1. Paralized muscles become flaccid due to loss of muscle tone.
2. Deep reflexes exaggerated & superficial reflexes lost.	2. Both superficial and deep reflexes lost.
3. Muscles are not wasted.	3. Muscles are degenerated & undergo wasting.
4. Babinski sign positive.	4. Babinski sign negative.

Release Phenomenon

Escape of lower motor neuron from the inhibitory impulses of upper motor neuron is called release phenomenon.

Normally, the upper motor neuron exerts inhibitory impulse to lower motor neuron for normal action. But in upper motor lesion they can't send inhibitory impulse to the lower motor neuron. So, the lower motor neurons are released from the inhibitory action of upper motor neuron. Then the activity of lower neuron is increased and muscle tone is increased.

Pain

Difinition : Pain is the protective mechanism of the body when any tissue is being damaged.

Types of pain :

a. Acute pain.

b. Slow pain.

Acute pain : It occurs within 0.1 sec when a pain stimulus is applied and is transmitted through type A delta pain fibres, other name of it sharp pain, pricking pain, fast pain.

Slow pain : It begins only after a seond. or more and then increases slowly over a period of many second and even minutes. It is transmitted through type C pain fibres. Other name : Burning pain, throbbing pain, aching pain.

(Ref. Guyton & Hall 11th edition)

Pain receptor : Free nerve ending.

Cause of pain :

1. Tissue damage.
2. Tissue ischemia.
3. Muscle spasm.
4. Irritation or over distension of viscera.

(Ref. Guyton & Hall 11th edition)

Referred Pain

i. *Definition* : Irritation of a viscus frequently produces pain that is felt not in the viscus but in some somatic region sharing the same segmental innervation. Such pain is said to be referred to the somatic structure.

   Deep somatic pain may also be referred, but superficial pain does not.

ii. *Explanation* : The explanation for referred pain is unknown. One theory is that the nerve fibres from the viscus and the dermatome ascend to the CNS along a common pathway, and the cerebral cortex is incapable of distinguishing between the sites of origin.

iii. *Mechanism (cause) of referred pain* :

   a. *Convergence theory* : Both somatic and visceral afferents converge on the same second order neuron that project to the brain. So when the same pathway is stimulated by visceral afferents the signal reaching the brain is no different and the pain is projected to the dermatome.

   b. *Facilitation theory* : Branches of the visceral pain fibres make synapse with the same spinothalamic neuron

receiving afferents from the somatic area. So, stimulation of visceral pain fibres causes sensation of pain in that somatic region.

iv. ***Examples of referred pain*** :

Pain originate	*Pain felt*
a. Cardiac (myocardial ischemia)	a. Left shoulder and upper arm Middle of the sternum.
b. Diaphragm	b. Shoulder tip.
c. Acute appendicitis	c. Periumblical region
d. Ureteric pain	d. Testicle
e. Renal pain	e. Directly behind the kidney
f. Peptic ulcere disease	f. Epigastrium
g. Pancreatic	g. Posterior abdominal wall directly behind the pancreas.

Q. 09. **Give the difference between visceral pain and somatic pain.**

Ans. Difference between visceral pain and somatic pain :

Visceral pain	*Somatic pain*
a. Poorly localized	a. Highly localized
b. Slow pain, unpleasant	b. Fast pain
c. Pass through C fibre Aδ & C fibre	c. Pass through
d. Asseciated with autonomic symptoms	d. Not associated with autonomic symptoms.
e. Often radiates or referred to other areas.	e. Do not referred

Pathway of pain and temperature

(also tickling & itching) :

i. *Receptor* :
   a. Pain receptor : Free nerve endings
   b. Temperature receptor :
      1. Cold receptor : End bulbs of krause
      2. Hot receptor : End organ of Ruffini's

ii. *Pathway* : Lateral spinothalamic tract.

iii. *Extension* : From the spinal cord to the thalamus and take position into opposite lateral funiculus.

iv. *Origin & course* :
   a. *1st order neuron :* Formed by the axons of the cells of dorsal root ganglia in the spinal cord. These fibres ends in the posterior horn cell of same side.
   b. *2nd order neuron :* These are the axons of the *nucleus centrodorsalis* of posterior horn, crosses the white comissure goes to the *lateral funiculus* of *opposite* side and ascend as *lateral spinothalamic* tract and finally terminate into the *ventrobasal nucleus* of thalamus and 3rd order neuron arises.
   c. *3rd order neuron :* These fibre terminate into the somatosensory area of cortex (Fig : 16-10).

Pathway of Crude touch

i. *Receptor* : Free nerve endings; Meissner's corpuscles

ii. *Pathway* : Anterior spinothalamic tract.

iii. *Extension* : From the spinal cord to the thalamus and take position into opposite anterior funiculus.

iv. *Origin & course* :
   a. *1st order neuron :* Formed by the axons of the cells of dorsal root ganglia in the spinal cord. These fibres ends in the posterior horn cell of same side.
   b. *2nd order neuron :* These are the axons of the *nucleus centrodorsalis* of posterior horn, crosses the white comissure goes to the *anterior funiculus* of *opposite* side and ascend as *anterior spinothalamic tract* and finally terminate into the *ventrobasal nucleus* of thalamus and 3rd order neuron arises.
   c. *3rd order neuron :* These fibre terminate into the somatosensory area of cortex (Fig : 16-10).

Pathway of Fine touch &

(sense of vibration, Kinesthetic sensation, tactile localization)

i. *Receptors* :
   a. Fine touch : Merkel's discs, expanded tip endings
   b. Tactile localization, sense of vibation, kinesthetic sensation : Free nerve endings, Expanded tip endings, (Merkel's discs, several other varients), Spray endings (Ruffini's endings), encapsulated endings (Meissner's corpuscles, krause's corpuscles.

ii. *Pathway* : Tract of Gall and tract of Burdach.

iii. *Origin and course* : Pl follow the tract of Gall and tract of Burdach (page 16.16).

Muscle tone

Muscle tone is a state of partial tetanus (tension) of the muscle during resting condition, maintained by continuous asynchronous discharge of impulses in the motor nerves suppling the muscle.

(Ref. Wright's 13th 297)

Importance of muscle tone :

1. It sets the bias for efficient willed movement

2. It sets the bias for the efficiencies of the reflex action.
3. It is also responsible for maintenance of posture.
4. It also helps in maintenance of form, texture and appearance, e.g look of subject.

Factors affecting muscle tone & posture :

1. Genesis of tone in the muscles at the segmental level.
2. Nociceptive and other factors influencing distribution of tone.
3. Supra spinal control-
   a. Role of cerebral cortex
   b. Role of cerebellum
   c. Role of hypothalamus.
   d. Role of corpus striatum
   e. Role of brain stem.
4. Role of labyrinthine and wrighting reflexes,
5. Role of drugs.
6. Role of sleep.

Mechanism of maintenance of muscle tone : The segmental spinal reflex is responsible for the tone in the muscle which develops following way-

1. *Firstly :* There is a fusiform or Gamma-efferent activity which is tonically discharging impulse to intrafusal fibres of muscle spindle. This causes contraction of intrafusal fibres leading to stretching of nuclear leaf, distorting the annulospiral endings and a receptor potential is set up.
2. *Secondly :* Receptor potential is changed to action potential and afferent discharges pass through annulospiral fibre as well as through flower spray fibres and are transmitted through posterior nerve root to spinal cord.
3. *Thirdly :* Afferent discharges from annulospiral fibre via monosynaptic path to lower motor neurons which results in muscular contraction a phasic reflex response. This release the tension of intrafusal fibres, abolishing the annulospiral discharges.
4. *Fourthly :* The annulospiral afferent discharge is followed by afferent discharges through Golgi-tendon fibres e. g. slow conducting discharges which slowly stimulate the alphamotor neuron for a more static reflex response. So, the contraction of extrafusal fibre is proportional to gamma-efferent activity and lasts as long as the activity lasts.

Causes of abolish of muscle tone :

1. By destroying the centre in the spinal cord.
2. By destroying the posterior root.
3. By destroying the anterior root.
4. By division of the pripheral nerve entering a muscle.
5. By transection of spinal cord.

Motor Unit

A motor neuron together with the group of muscle fibres which it innervates is called a motor unit. A ventral horn cell & its efferent fibre is a motor neuron. The size of the motor unit varies inversely with the precision of the movements performed by the part; e.g. in the limb muscles the unit may contain up to 2000 muscle fibres, in the extrinsic eye muscles less than 5.

(Ref. Wright's, 13th page- 255)

Motor neuron pool : Several anterior horn cells of spinal cord or their homologus, join together to carry out the order for a particular action. They constitute the motor neuron pool.

Muscle spindle

It is a special type of receptor present within the muscle fibre. Each muscle spindle consist of two to ten bundle of muscle

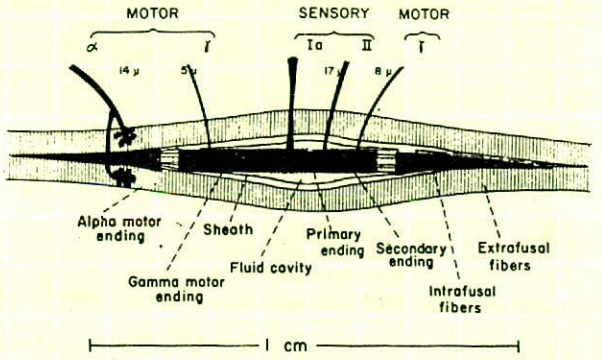


Fig. 16-14. *Muscle Spindle.*

fibres enclosed within a capsule. The capsule is tapered at both ends. The modified muscle fibre within this capsule is known as interfusal muscle fibre which are arranged in two groups-

i. *Nuclear bag fibres :* Displaying an aggregation of nuclei at the equatorial plane.

ii. *Nuclear chain fibres :* Displaying a single row of nuclei in a chain of muscle fibre.

Each muscle spindle is innervated by sensory and motor nerve fibre. The sensory innervation is of two types-

a. Primary or Annulospiral ending placed at centre.
b. Secondary or flowerspray ending on both side of the primary ending.

The motor terminal are of three types-two gamma efferent fibre and one β-efferent fibre.

Innervation of muscle spindle : Each muscle spindle is innervated by sensory and motor nerve fibre.

1. *Sensory innervation* :
   a. Primary or annulospiral ending placed at centre.
   b. Secondary or flowerspray ending on both side of the primary ending..
2. *Motor innervation* : The motor terminal are of three types :

a. Two gamma-efferent fibres.
b. One beta-efferent fibre.

Functions of muscle spindle :

1. Responsible for stretch reflex during muscle contraction.
2. Maintains muscle tone
3. Maintains posture
4. Carries kinesthetic sensation
5. Mediates protective reflex when muscle vigorously contract.

Golgi tendon organs

(Neurotendinous spindles)

i. *Definition* : Neurotendinous spindles are specialized sense organs present in muscle tendon providing information about muscle tension.

ii. *Location* : At the junction of tendon with muscle.

iii. *Structure* : Golgi tendon organs consists of a net-like collection of knobby nerve endings among the fascicles of a tendon.

iv. *Innerevation* : Ib group of myelinated rapidly conducting sensory nerve fibres.

v. *Mechenism of action* : Stimulation of these Ib fibers leads to the production of IPSPs on the motor neurons that supply the muscle from which the fibers arise. The nerve endings are activated when tension develops in the tendon- thus neurotendinous spindle detects change in muscle tension.

vi. *Function* : Provide information about muscle tension to the CNS and thus influence voluntary muscle activity.

(Ref. Ganong 22th Edition: page 133)

Q. 00. **Compare between the muscle spindle and Golgi tendon organ.**

Ans. Comparison between muscle spindle and golgi tendon organ :

Muscle spindle	*Golgi tendon organ*
a. Present within muscle fibres	a. Present in muscle-tendon junction.
b. Sensory fibres are both I (alpha) and II (gamma) type.	b. Sensory fibres are Ib group type.
c. Regulates velocity of muscle contraction and muscle length.	c. Regulates muscle tension
d. Muscle spindle reflexes are excitatory	d. Golgi tendon reflexes are inhibitory.

Cerebral cortex

Definition : Cerebral cortex forms a complete covering of the cerebral hemisphere and is composed of gray matter.

Total number of neuron : The cerebral cortex contain approximately 10 billions neurons.

Types of nerve cells in cerebral cortex :

a. Pyramidal cells
b. Stellate cells
c. Fusiform cells
d. Horizontal cells of Cajal
e. Cells of Martinotti.

Layers of the cerebral cortex : There are six layers in the cerebral cortex :

i. *Molecular layer (plexiforrn layer)* : This is the most superficial layer; it consists rnainly of a dense network of tangentially oriented *nerve fibers*. These fibers are derived from the apical dendrites of the pyramidal cells and fusiform cells, the axons of the stellate cells, and the cells of Martinotti. Afferent fibers originating in the thalamus and in association with commissural fibers also are present. Scattered among these nerve fibers are occasional horizontal cells of Cajal.

This most superficial layer of the cortex clearly is where large numbers of synapses between different neurons occur.

2. *External granular layer* : This layer contains large numbers of *small pyramidal cells* and *stellate cells*. The dendrites of these cells terminate in the molecular layer, and the axons enter deeper layers where they terminate or pass on to enter the white matter of the cerebral hemisphere.

3. *External pyramidal layer* : This layer is composed of *pyramidal cells*, whose cell body size increases from the superficial to the deeper borders of the layer. The apical dendrites pass into the molecular layer and the axons enter the white matter as projection, association, or commissural fibers.

4. *Internal granular layer* : This layer is composed of closely packed stellate cells. There is a high concentration of horizontally arranged fibers known collectively as the *external band of Baillarger.*

5. *Ganglionic layer (internal pyramidal layer)* : This layer contains very *large and medium-size pyramidal cells*. Scattered among the pyramidal cells are *stellate cells* and cells of *Martinotti*. In addition, there are a large number of horizontally arranged fibers that form the *inner band of Baillarger*. In the motor cortex of the precentral gyrus, the pyramidal cells of this layer are very large and are known as Betz cells. These cells account for about 3 percent of the projection fibers of the *corticospinal* or *pyramidal tracts*.

The cerebellum and its connections :

The afferent cerebellar pathways :

Pathway	*Function*	*Origin*	*Destination*
Corticopontocerebellar	Conveys control from cerebral cortex	Frontal, parietol, temporal, and occipital lobes	Via pontine nuclei and mussy fibers to cerebellar cortex
Cerebro-olivocerebellar	Conveys control from cerebral cortex	Frontal, parietal. temporal, and occipital lobes	Via inferior olivary nuclei and climbing fibers to cerebelar cortex
Cerebroreticuloeerebellar	Conveys control from cerebral cortex	Sensorimotor areas	Via reticular forniatmon
Anterior spinocerebellar	Conveys information from muscles and joints	Muscle spindles, tendon organs, and joint receptors	Via mossy fibers to cerebe]lar cortex
Posterior spinocerebellar	Conveys information from muscles and joints	Muscle spindles, tendon organs, and joint receptors	Via mossy fibers to cerebellar cortex
Coneocerebellar	Conveys information from muscles and joints of upper limb	Muscle spindles, tendon organs, and joint receptors	via mossy fibers to cerebellar cortex
vestibu!ar nerve	Conveys information of head position and movement	Ulricle, saccole, and semicrcufar canals	Via mossy fibers to cortex of flocculonodular lobe
Other afferents	Conveys information from midbrain.	Red nucleus, teclum	Cerehellar cortex

(Clinical Neuroanatomy 5th Edition; page 236)

The efferent cerebellar pathways :

Pathway	*Function*	*Origin*	*Destination*
Globose-emboliform-rubral	Influences ipsilateral motor activity	Globose and emboli-form nuclei	To contralateral red nucleus, then via crossed rubrospinal tract to ipsilat-eral motor neurons in spinal cord.
Dentothalamic	Influences ipsilateral motor activity	Dentate nucleus	To contralateral ventrolateral nucleus of thalamus, then to contralateral motor cerebral cortex; corti-cospinal tract crosses midline and controls ipsilateral motor neurons in spinal cord.
Fastigial vestibular	Influences ipsilateral extensor muscle tone	Fastigial nucleus	Mainly to ipsilateral and to.contralat-eral lateral vestibular nuclei; vestibulospinal tract to ipsilateral motor neurons in spinal gord.
Fastigial reticular	Influences ipsilateral muscle tone	Fastigial nucleus	To neurons of reticular formation; reticulospinal tract to ipsilateral motor neurons to spinal cord.

Note that each cerehellar hemisphere influences the voluntary muscle tone on the same side of he body.

(Clinical Neuroanatomy 5th Edition; page 238)

6. *Multiform layer (layer of polymorphic cells)* : Although the majority of the cells are *fusiform*, many of the cells are *modified pyramidal cells*, whose cell bodies are triangular or ovoid. The cells of *Martinotti* also are conspicuous in this layer. Many nerve fibers are present that are entering or are leaving the underlying white matter.

(Clinical Neuroanatomy 5th Edition; page 284)

Motor system

Name (list) the motor systems :

The motor system comprises-

i. Cerebral cortex (cortical motor area)
ii. Pyramidal system
iii. Extrapyramidal system
iv. Cerebellum
v. Spinal motor neurons i.e. anterior horn cells and homogenous neurons in the motor nuclei of the cranial nerves (these neurons are the final common paths to motor system).

Function of motor system

The function of the motor system are :

a. Control of posture and movement
b. Reflex activities i.e. swallowing, chewing, micturation etc.

General motor control scheme

a. *Planning of movement* occurs in the cortex, basal ganglia, and lateral portion of the cerebellar hemisphere (neocerebellum).
b. *Commands* for voluntary movement originate in cortical association area.
c. *Relay* of command to final common paths via corticospinal and corticobulbar system.
d. *Execution* of commands by the motor neurons in the brain stem and spinal cord i.e. anterior horn cells.
e. *Adjustment* of movement by the medial and intermediate portions of the cerebellum.

Motor area of the cerebral cortex

Cortical motor areas : Brodmann described the division of the cerebral cortex into different area of specialization. The motor cortical area include :

a. Primary motor area (Brodmann's area 4) : Responsible for motor execution.
b. Premotor cortex (Brodmann's area 6 and part of 8, 44, 45 : It programs the activity of the primary cortex i.e. design the pattern of movement.
c. Supplementary motor area : Planning the movement.

Cerebellum

Nuclei of cerebellum : The cerebellum has an external cerebellar cortex (gray matter) and inner white matter within which lie deep intracerebellar nuclei.

a. *The cerebellar cortrical cells* :
   i. Stellate cells and basket cells in external molecular layers.
   ii. Purkinje cells : are large Golgi type I neurons in middle layer i.e purkinjee cell layer.
   iii. Golgi cells : In inner granular layer.

   The Purkinjee cells are among the biggest neurons in the body. Their axons constitute the only output from the cerebellar cortex (make synapse with deep cerebellar nuclei)- exert inhibitory effects on the intracerebellar nuclei. The stellate cells, basket cells and Golgi cells serve as inhibitory interneurons.

b. *Deep intracerebellar nuclei* : They are the functional unit of cerebellum. These are-
   i. Dentate nucleus (most laterally) : largest ccrebellar nucleus
   ii. Emboliform nucleus
   iii. Nucleus globose
   iv. Fastigial nucleus.

Vestibulocerebellum

i. *Structure* : Composed of flocculonodular lobe and nodule of the vermis :
ii. *Connection* :
   a. *Afferent connection* : From the vestibular nerve and vestibular nuclei.
   b. *Efferent pathway* : Transmitted through the vestibulospinal, and reticulospinal tracts.
iii. *Function* : Assists in maintaining of equilibrium by bringing about modification in muscle tone.
iv. *Lesion* : produces disorder in equilibrium.

Spinocerebellum

i. *Structure* : Composed of pyramid of the vermis and adjacent medial portions of the hemisphere.
ii. *Connection* :
   a. *Afferent connection* : Receives input from the proprioceptive endings in muscles and tendons, and from touch and pressure receptors (spinocerebellar tracts, cuneocerebellar fibres, and reticulocerebellar tracts).
   b. *Efferent pathway* : Transmitted through the vestibulospinal and reticulospinal tracts.
iii. *Function* : Play an active role in the maintenance of posture and the performance of voluntary movements.
iv. *Lesion* : Produces disorder in gait.

Neocerebellum

i. Structure : Composed of lateral portion of the cerebellar hemisphere.

ii. *Connection* :
   a. *Afferent connection* : Receives a very large input through the corticopontocerebellar tracts from the cerebral cortex of the opposite side.
   b. *Efferent pathway* : Transmitted through the thalamus to the motor area of the cerebral cortex, then through the corticospinal and corticonuclear fibres to the lower motor neurons.

iii. *Function* : Facilitates a smooth, coordinated voluntary movement and ensure that the force, direction, and extent of the movement are accurate i.e. planning and programming of the movements.

iv. *Lesion* : Hypotonia, intention tremor.

Q. 00. **Briefly describe the cerebelllar afferent and efferent fibres.**

Ans. Cerebellar afferent and efferent fibres :

Cerebellar afferent fibres :
   a. *Types* :
      i. Climbing fibres : The climbing fibres are the terminal fibres of the olivocerebellar tracts.
      ii. Mossy fibres : The mossy fibres are the terminal fibres of all other cerebellar afferent tracts.
   b. Cerebellum receives afferent fibres from the :
      i. Cerebral cortex
      ii. Spinal cord
      iii. Vestihular nuclei
      iv. Red nucleus, tectum.

Cerebellar efferent fibres : The entire output of the cerebellar cortex is through the axons of the purkinjee cells. The efferent outflow of the cerebellum destined to :
   i. Globose and emboliform nucleus →Red nucleus → ipsilateral anterior horn cells of the spinal cord (reticulospinal tract).
   ii. Dentate nucleus → Thalamus → motor cortex → ipsilateral motor neurons in spinal cord.
   iii. Fastigial nucleus → Vestibular nucleus → ipsilateral motor neurons in spinal cord (vestibulospinal tract).
   iv. Fastigial nucleus → Reticular formation → ipsilateral motor neurons in spinal cord (reticulospinal tract).

Function of cerebellum

1. It maintains the tone, posture and equilibrium.
   a. It maintains tone through higher cortical and lower spinal centre by excitatory and inhibitory control.
   b. By adjusting the distribution of tone in postural muscle, it maintains the errect posture.
   c. It maintains the equilibrium of the body in standing, jumping, running by adjusting the muscle which are responsible for this purpose.
2. It co-ordinates the voluntary movements.
3. It makes the movement smooth and nonauscilatory.
4. It contributes the range, force, speed and direction of movement for the purpose.

Q. 06. **What is cerebro-cerebellar feed back mechanism**?

Ans. Cerebro-cerebellar feed back mechanism :

i. The mechanism by which the cerebellum controls the activity of motor cortex is called cerebro-cerebellar feed back mechanism or error control mechanism.

ii. During voluntary movements impulse from the cerebral cortex to the muscle spindle comes via corticospinal tract.

iii. At the same time a collateral branceh goes to the cerebellum via fronto-pontocerebellar tract.

iv. The cerebllum also gets impulse from the muscle spindle through the spinocerebellar tract. Then from the cerebellum impulse goes to the thalamus and then goes through the dento-rubro-corticothalamic tract to the cerebral cortex.

Generally motor cortex send impulse to the muscle more than required. Then cerebellum automatically inhibit the cerebral cortex after calculating appropriate time and movement required to reach to the point of intention.

(Q. What is error control by cerebellum?)

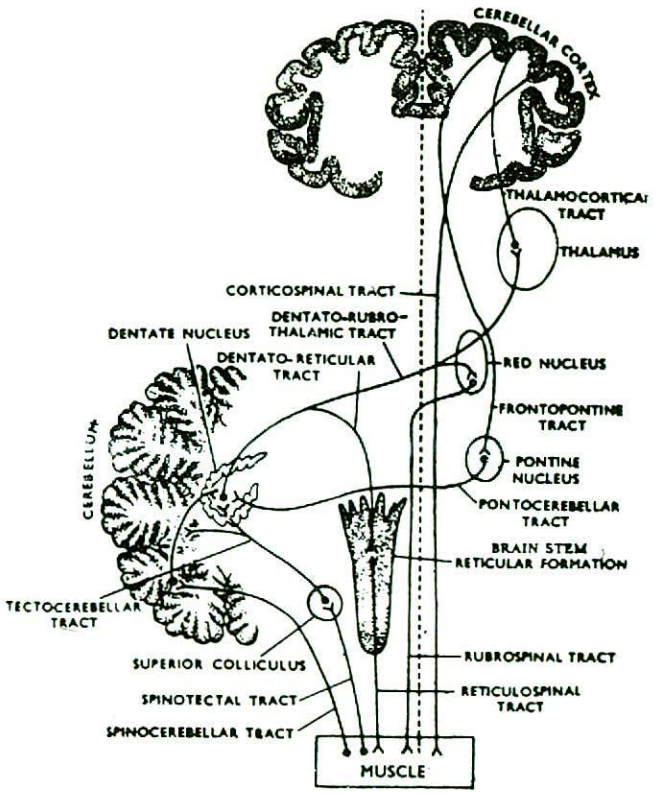


Fig. 16-15. *Schematic reprensentation of the cerebellar feadback system.*

Q. 04. ***Describe how cerebellum controls equilibrium.**

Ans. Control of equilibrium by cerebellum :

i. During the control of equilibrium, it is presumed that the information from both the body periphery and the vestibular apparatus is used in a typical feedback control circuit to provide *anticipatory correction* of postural motor signals as necessary for maintaining equilibrium even during extremely rapid motion, including rapidly changing directions of motion.

ii. The feedback signals from the peripheral areas of the body help in this process.

iii. Their help is mediated mainly through the *cerebellar vermis* that functions in association with the axial and girdle muscles of the body.

iv. It is the role of the vestibulocerebellum to help the brain stem vestibular and reticular nuclei compute the required positions of the respective parts of the body at any given time, despite the long delay time for passage of sensory signals from the periphery to the cerebellum.

(Ref. Guyton & Hall 11th Edition; page 704)

Posture

Q. 02. **What is posture**?

Ans. Posture :

i. *Definition* : Posture may be defined as the position adopted by the individual within his or her environment.

In standing posture the line of gravity passes through the odontoid process of the axis, behind the centers of the hip joints, and in front of the knee and ankle joints.

Q. 02. **What are the posture-regulating systems**?

Ans. Posture-regulating systems are : The posture of an individual depends on the degree and distribution of muscle tone.

Posture is maintained by the :

i. Integrity of the reflex arc

ii. Nervous input from higher levels of the nervous system received by the lower motor neuron i.e
   a. Vestibular apparatus
   b. Cerebral centres, midbrain and cerebellum
   c. Visual centres
   d. Reticular activating system.

iii. General information arising from other muscle groups and joints (proprioception).

Signs of cerebellar lesions

In cerebellar lesions two types of disturbance occur :

1. Disturbance of posture.
2. Disturbance of voluntary movement.

1. *Disturbance of posture* :
   a. *Atonia* : Loss of muscle tone.
   b. *Nystagmus* : Tremor of eye ball when viewing towards a same place.
   c. *Deep reflexes* : Characterstically pendular.

2. *Disturbance in voluntary movement* :
   a. *Ashthenic movement* : Movement will be weak.
   b. *Ataxia* : It means incoordination of movement.
      i. Decomposition of movement : Movement will take place in obvious stage.
      ii. Asynergia : Means lack of cordination between protogonist, antagonist and synergist.
      iii. Dysmetria : Movement will overshoot the intended mark.
   c. *Intention tremor* : Jerking of organ or tremor during voluntary work.
   d. *Gait* : Gait will be deviated towards the affected side then again bring himself towards the previous side.
   e. *Speech* : It will be scanning and sluggish.
   f. *Adiadochokinesis* : Inability to perform rapid pronation and supination.

Test for cerebellar lesion

i. Finger nose test
ii. Adiadochokinesis
iii. Gait test
iv. Speech test.

Paralysis

Temporary suspension or permanent loss of function, specially loss of sensation or voluntary motion is called paralysis,

Types :

1. *Spastic paralysis* : The paralysis due to the lesions of upper motor neurons is called spastic paralysis.
2. *Flaccid paralysis* :The paralysis due to the lesions of lower motor neurons of spinal cord is called flaccid paralysis.

Difference between spastic and flaccid paralysis

Spastic paralysis	*Flaccid paralysis*
1. Paralized muscles are rigid due to increase muscle tone (spastic paralysis).	1. Paralized muscles become flaccid due to loss of muscle tone. (flaccid paralysis)
2. Deep reflexes exaggerated & superficial reflexes lost.	2. Both superficial and deep reflexes lost.
3. Muscles are not wasted.	3. Muscles are degenerated and under go wasting.
4. Babinski sign positive.	4. Babinski sign negative.

Thalamus

Function of the thalamus

Although an enormous amount of research has been devoted to this area, we still know very little about the functional significance of many of the nuclei.

The following basic principles should be committed to memory :

1. The thalamus is made up of complicated collections of nerve cells that are centrally placed in the brain and are interconnected
2. A vast amount of sensory information of all types (except smell) converges on the thalamus and presumably is presumably integrated through the interconnections between the nuclei. The resulting information pattern is distributed to other parts of the central nervous system. It is probable that olfactory information is first integrated at a lower level with taste and other sensations and is relayed to the thalamus from the amygdaloid complex and hippocampus through the marnmillothalamic tract.
3. Anatomically and functionally, the thalamus and the cerebral cortex are closely linked. The fiber connections have been established, and it is known that following

Table : **The various thalamic nuclei, their nervous connections, and their functions**

Thalamlc nucleus	*Afferent neuronal loop*	*Efferent Neuronal loop*	*Function*
Anterior	Mammillothalamic tract, cingulate gyrus, hypothalamus	Cingulate gyrus, hypothalamus	Emotional tone, mechanisms of recent memory
Dorsomedial	Prefrontal cortex, hypothalamus, other thalamic nuclei	Prefrontal cortex, hypothalamus, other thalamic nuclei	Integration of somatic, visceral, and olfactory information and relation to emotional feelings and subjective states
Lateral dorsal, lateral posterior, pulvinar	Cerebral cortex, other thalamic nuclei	Cerebralcortex, other thalamic nuclei	Unknown
Ventral anterior	Reticular formation, substantia nigra, corpus striatum, premotor cortex, other thalamic nuclei	Reticular formation, substantia nigra, corpus striatum, premotor cortex, other thalamic nuclei	Influences activity of motor cortex
Ventral lateral	As in ventral anterior nucleus but also major input from cerebellum and minor input from red nucleus		Influences motor activity of motor cortex
Ventral posteromedial(VPM)	Trigeminal leminiscus, gustatory fibers	Primary somatic sensory (areas 3, 1, and 2) cortex	Relays common sensations to consciousness
Ventral posterolateral (VPL)	Medial and spinal lemnisci	Primary somatic sensors' (areas 3, 1, and 2) cortex	Relays common sensations to consciousness
Intralaminar	Reticular formation, spinothalamic and trigeminothalamic tracts	To cerebral cortex via other thalamic nuclei, corpus striatum	Influences levels of consciousness and alertness
Midline	Reticular formation	Unknown	Unknown
Reticular	Cerebral cortex, reticular fornation	Other thalamic nuclei	? Cerebral cortex regulates thalamus
Medial geniculate body	Inferior colliculus, lateral lemniscus from both ears but predominantly the contralateral ear	Auditory radiation to superior temporal gyrus	Hearing
Lateral geniculate body	Optic tract	Optic radiation to visual cortex of occipital lobe	Visual information from opposite field of vision

(Clinical Neuroanatomy 5th Edition; page374)

removal of the cortex the thalamus can appreciate crude sensations. However, the cerebral cortex is required for the interpretation of sensations based on past experiences. For example, if the sensory cortex is destroyed, one can still appreciate the presence of a hot object in the hand; however, appreciation of the shape, weight, and exact temperature of the object would be impaired.

4. The thalamus possesses certain very important nuclei whose connections have been clearly established. These include the ventral posteromedial nucleus, the ventral posterolateral nucleus, the medial geniculate body and the lateral geniculate body. Their positions and connections should be learned.
5. The ventroanterior and the ventrolateral nuclei of the thalamus form part of the basal nuclei circuit and thus are involved in the performance of voluntary movements. These nuclei receive input from the globus pallidus and send fibers to the prefrontal, supplemental, and premotor areas of the cerebral cortex.
6. The large dorsomedial nucleus has extensive connections with the frontal lobe cortex and hypothalamus. There is considerable evidence that this nucleus lies on the pathway that is concerned with subjective feeling states and the personality of the individual.
7. The initralaminar nuclei are closely connected with the activities of the reticular formation and they receive much of their information from this source. Their strategic position enables them to control the level of overall activity of the cerebral cortex. The intralaminar nuclei are thus able to influence the levels of consciousness and alertness in an individual.

(Clinical Neuroanatomy 5th Edition; page 375, 376)

Thalamic syndrom

i. Disturbance in sensation
ii. Loss of tactile and thermal sensation
iii. Sensory ataxia
iv. Hemiplegia with hyperaesthesia
v. Severe spontaneous pain.

Hypothalamus

Nucleus of hypothalamus : Hypothalamus is divides into three zones.

1. *Periventicular zone :*
   i. Part of preoptic.
   ii. Suprachiasmatic.
   iii. Paraventricular.
   iv. Infundibular.
   v. Posterior group.
2. *Intermediate zone :*
   i. Part of preoptic.
   ii. Anterior group.
   iii. Dorsomedial.
   iv. Ventromedial.
   v. Premamillary.
3. *Lateral zone :*
   i. Part of preoptic.
   ii. Supraoptic.
   iii. Lateral group.
   iv. Tuberomamillary.
   v. Lateral tuberal.

(Ref. Gray's Anatomy)

Function of Hypothalamus

1. *Endocrine control :* With the help of releasing or inhibitory factors, it regulates the secretion of different endocrine gland.
2. *Neurosecretion :* Supraoptic and paraventicular nucleus secrete ADH and oxytocin.
3. *General autonomic effect :* Anterior hypothalamus mediates the parasympathetic activity and the posterior part mediate the sympathetic activity. Thus it regulates the CVS, respiratory and alimentary functions.
4. *Temperature regulation :* Cold sensative area exists in anterior part and heat sensative area exist in posterior part-by which it regulates body temperature.
5. *Regulation of food and water intake :* Hunger center is placed laterally, the satiety center is medially by which it regulates food and water intake.
6. *Sexual behaviour and reproduction :* It control sexual function and reproductive cycle through gonadotropin production.

Afferent & efferent connections of the hypothalamus

The principal afferent and efferent neural pathways to and from the hypothalamus are mostly unmyelinated. Many connect the hypothalamus to the limbic system. There are also important connections between the hypothalamus and nuclei in the midbrain tegmentum, pons, and hindbrain.

Norepinephrine-secreting neurons with their cell bodies in the hindbrain end in many different parts of the hypothalamus. Paraventricular neurons that probably secrete oxytocin and vasopressin project in turn to the hindbrain and the spinal cord. Neurons that secrete epinephrine have their cell bodies in the hindbrain and end in the ventral hypothalamus.

There is an intrahypothalamic system of dopamine-secreting neurons which have their cell bodies in the arcuate nucleus and end on or near the capillaries that form the portal vessels in the median eminence. Serotonin-secreting neurons project to the hypothalamus from the raphe nuclei.

(Ref. Ganong 22th Edition; page233)

Table. **Summary of principal hypothalamic regulatory mechanisms** :

Function	*Afferents from*	*Intearating areas*
Temperature regulation	Temperature receptors in the skin, deep tissues, spinal cord, hypothalamus, and other parts of the brain	Anterior hypothalamus, response to heat; posterior hypothalamus, response to cold
Neuroendocrine control of :		
Catecholamines	Limbic areas concerned with emotion	Dorsal and posterior hypothalamus
Vasopressin	Osmoreceptors, *volume receptors*, others	Supraoptic and paraventricular nuclei
Oxytocin	Touch receptors in breast, uterus, genitalia	Supraoptic and paraventricular nuclei
Thyroid-stimulating hormone (thyrotropin,TSH) via TRH	Temperature receptors in infants, perhaps others	Paraventricular nuclei and neighboring areas
Adrenocorticotropic hormone (ACTH) and β-lipotropin (β-LPH) via CRH	Limbic system (emotional stimuli); reticular formation ('systemic stimuli); hypothalamic and anterior pituitary cells sensitive to circulating blood cortisol level; suprachiasmatic nuclei (diurnal rhythm)	Paraventricular nuclei
Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) via GnRH	Hypothalamic cells sensitive to estrogens, eyes, touch receptors in skin and genitalia of reflex ovulating species	Preoptic area; other areas
Prolactin via PIH and PRH	Touch receptors in breasts, other unknown receptors	Arcuate nucleus; other areas (hypothalamus inhibits secretion)
Growth hormone via somatostatin and GRH	Unknown receptors	Periventricular nucleus, arcuate nucleus
Appetitive behavior		
Thirst	Osmoreceptors, probably located in the organum vasculosum of the lamina terminalis; angiotensin II uptake in the subfornical organ	Lateral superior hypothalamus
Hunger	Glucostat cells sensitive to rate of glucose utilization; leptin receptors; receptors for other polypeptides	Ventromedial, arcuate, and paraven - tricular nuclei; lateral hypothalamus
Sexual behavior	Cells sensitive to circulating estrogen and androgen, others	Anterior ventral hypothalamus plus, in the male, piriform cortex
Defensive reactions (fear, rage)	Sense organs and neocortex, paths unknown	Diffuse, in limbic system and hypothalamus
Control ot body rhythms	Retina via retinohypothalamic fibers	Suprachiasmatic nuclei.

(Ref. Ganong 22th Edition; page 236)

Q. 02. **Mention the endocrine functions of hypothalamus.**

Ans. *Endocrine control :* With the help of releasing or inhibitory factors, it regulates the secretion of different endocrine gland.

It secretes :

i. Catecholamines
ii. Vasopressin
iii. Oxytocin
iv. Thyroid-stimulating hormone (thyrotropin,TSH) via TRH
v. Adrenocorticotropic hormone (ACTH) and β-lipotropin (β-LPH) via CRH
vi. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) via GnRH
vii. Prolactin via PIH and PRH
viii. Growth hormone via somatostatin and GRH.

Basal ganglia

Anatomic considerations : The term basal ganglia is generally applied to five structures on each side of the brain :

a. Three large nuclear masses underlying the cortical mantle :
   i. Caudate nucleus
   ii. Putamen
   iii. Globus pallidus : The globus pallidus is divided into an external and an internal segment.
b. Others :
   iv. Functionally related subthalamic nucleus (Body of Luys)
   v. Substantia nigra : The substantia nigra is divided into a pars compacta and a pars reticulata.

The caudate nucleus and the putamen are frequently called the *striaturn*; the putamen and the globus pallidus are sometimes called the *lenticular nucleus*.

Parts of the thalamus are intimately related to the basal ganglia.

(Ref. Ganong 22th Edition; page213)

Connections of the basal ganglia :

I. *Afferent connections* :
   i. The main afferent connections to the basal ganglia terminate in the striatum. They include the-
      a. Corticostriate projection from all parts of the cerebral cortex.
      b. There is also a projection from the centromedian nucleus of the thalamus to the striatum.
   ii. *The connections between the parts of the basal ganglia* : They include-
      a. A dopaminergic nigrostriatal projection from the pars compacta of the substantia nigra to the striatum.
      b. A GABAergic projection from the striatum to the pars reticulata of the substantia nigra.

   The caudate nucleus and the putamen project to both segments of the globus pallidus. The external segment of the globus pallidus projects to the subthalamic nucleus, which in turn projects to both segments of the globus pallidus and the substantia nigra.

II. *Efferent connections* : The principal output from the basal ganglia is from the-
   i. Internal segment of the globus pallidus via the *thalamic fasciculus* to the ventral lateral, ventral anterior and centromedian nuclei of the thalamus.
   ii. From the thalamic nuclei, fibers project to the prefrontal and premotor cortex.
   iii. The substantia nigra also projects to the thalamus.
   iv. There are a few additional projections to the habenula and the superior colliculus.

However, the main feature of the connections of the basal ganglia is that the cerebral cortex projects to the striatum, the striatum to the internal segment of the globus pallidus, the internal segment of the globus pallidus to the thalamus, and the thalamus back to the cortex, completing a loop.

The output from the internal segment of the globus pallidus to the thalamus is *inhibitory*, whereas the output from the thalamus to the cerebral cortex is *excitatory*.

The striatum is made up of a unique mosaic of patches or striosomes composed of nerve endings in a matrix that receives other endings. The neurons of the corticostriate projection that originate in the deep portion of layer 5 of the cortex terminate in the patches, whereas the neurons that originate in layers 2 and 3 and the superficial part of layer 5 end primarily in the matrix. Neurons with their cell bodies in patches project in large part to dopaminergic neurons in the pars compacta of the substantia nigra, whereas many of the neurons with their cell bodies in the matrix project to GABAergic neurons in the pars reticulata of the substantia nigra.

However, the physiologic significance of these connections is uncertain.

(Ref. Ganong 22th Edition; page 213, 214)

Metabolic considerations of basal ganglia : The metabolism of the basal ganglia is unique in a number of ways. These structures have a high O_2 consumption. The copper content of the substantia nigra and the nearby locus ceruleus is particularly high. In Wilson's disease, a genetic autosomal recessive disorder of copper metabolism in which the plasma level of the copper-binding protein cerulo- plasmin is usually low, there is chronic copper intoxication and severe degeneration of the lenticular nucleus.

(Ref. Ganong 22th Edition; page 214)

Function of basal ganglia : Our knowledge of the precise functions of the basal ganglia is still rudimentary.

Basal ganglia are involved in the *planning* and *programming* of movement or, more broadly, in the processes by which an *abstract thought* is converted into *voluntary action*.

They discharge via the thalamus to areas related to the motor cortex, and the corticospinal pathways provide the final common pathway to the motor neurons. In addition, the field potentials in the basal ganglia oscillate, and it has been suggested that the oscillations may have functions like the putative functions of the oscillations of the thalamocortical circuits.

The basal ganglia also play a role in sonic cognitive processes, and these are particularly the province of the caudate nucleus.

(Ref. Ganong 22th Edition; page 214)

Diseases of the basal ganglia in humans : Disorders of movement associated with diseases of the basal ganglia in humans are of two general types :

i. *Hyperkinetic* : The hyperkinetic conditions, those in which there is excessive and abnormal movement, include-
   a. Chorea
   b. Athetosis
   c. Hallism.

ii. *Hypokinetic* : Hypokinetic abnormalities include-
   a. Akinesia
   b. Bradykinesia.

Chorea is characterized by rapid, involuntary *dancing* movements.

Athetosis is characterized by continuous, slow writhing movements.

Choreiform and atherotic movements have been likened to the start of voluntary movements occurring in an involuntary, disorganized way. In ballism, there are involuntary movements that are flailing, intense, and violent.

Akinesia is difficulty in initiating movement and decreased spontaneous movement.

Bradykinesia is slowness of movement.

(Ref. Ganong 22th Edition; page214, 215)

Parkinsons disease

i. *Pathophysiology* : The disease is associated with progressive neuronal degeneration in the substantia nigra. The degeneration of the neurons of the substantia nigra that send their axons to the corpus striatum results in a reduction in the release of dopamine within the corpus striatum. This lead to hypersensitivity of the dopamine receptors in the postsynaptic neurons in the striatum. Clinical appearance of patients with the *shaking palsy*.

ii. *Age group* : 45 to 55.

iii. *Characteristics* :
   a. Reduction in movement, i.e. bradykinesia or akinesia
   b. Involuntary movements i.e. tremor, chorea, dystonia
   c. Rigidity.

iv. *Causes* :
   a. Idiopathic
   b. Drug e.g. phenothiazine
   c. MPTP can destroy substantia nigra
   d. Postencephalitic parkinsonism.

v. *Symptoms* :
   a. Tremor (resting); disappears during sleep.
   b. Bradykinesia i.e. difficulty in rising from a chair or getting into or out of bed.
   c. Micrographia i.e. small writing
   d. Limbs feel stiff
   e. Difficulties in fine movements.

vi. *Signs* :
   a. *Tremor* (4-7 Hz rest tremor)
   b. *Pill-rolling* movements of the fingers
   c. *Rigidity (lead-pipe rigidity and Cogwheeling)*
   d. Akinesia
   e. Expressionless face
   f. Postural changes i.e patient stands with a stoop
   g. Short, shuffling, and festinating gait
   h. Speech is monotonous, slurring dysarthria.

vii. *Treatment* :
   a. Dopamine agonist
   b. Anticholinergic drugs.

(Q. State the clinical features of perkinsonism)

Wilson's disease

i. *Pathophysiology* : This is a disease of abnormal copper metabolism. There is deposition of copper in the brain particularly in the basal ganglia that leads to degeneration of basal ganglia, in the cornea and in the liver.

ii. *Causes* :
   a. Failure to excrete copper
   b. Low serum ceruloplasmin (copper binding protein).

iii. *Neurological problems* : The neurological problems associated with Wilson's disease are :
   a. Tremor
   b. Dysarthria
   c. Involuntary movements
   d. Dementia.

iii. *Signs* :

Kayser-Fleischer ring : It is a specific sign for wilson's disease and which is due to copper deposition in Descemet's membrane in the cornea.

It appears as a ***greenish brown pigment*** at the selerocorneal junction just within the cornea.

Hunger

Feeding & satiety : Body weight depends on the balance between caloric intake and utilization of calories. Obesity results when the former exceeds the latter.

Food intake is regulated not only on a meal-to-meal basis but also in a way that generally maintains weight at a given set point. Dieters can lose weight when caloric intake is reduced but when they discontinue their diets, 95% of them regain the weight they lost. Similarly, during recovery from illness, food intake is increased in a *catch-up* fashion until lost weight is regained.

Role of the hypothalamus : Hypothalamic regulation of the appetite for food depends primarily upon the interaction of two areas :

i. A lateral *feeding center* in the bed nucleus of the medial forebrain bundle at its junction with the pallidohypothalamic fibers. Stimulation of the feeding center evokes eating behavior in conscious animals, and its destruction causes severe, fatal anorexia in otherwise healthy animals.

ii. A medial *satiety center* in the ventrornedial nucleus. Stimulation of the ventromedial nucleus causes cessation of eating, whereas lesions in this region cause hyperphagia and, if the food supply is abundant, the syndrome of *hypothalamic obesity*.

(Ref. Ganong 22th Edition; page 235, 237)

Other factors affecting food intake

i. *Temperature* : Food intake is increased in cold weather and decreased in warm weather. However, there is little evidence that body temperature is a major regulator of food intake.

ii. *Gastrointestinal tract* : Distention of the gastrointestinal tract inhibits appetite, and contractions of an empty stomach (*hunger contractions*) stimulate appetite, but denervation of the stomach and intestines does not affect the amount of food eaten.

iii. Cultural factors

iv. Environment

v. Past experiences related to the sight, smell, and taste of food also affect food intake.

Brown fat, a special form of body fat that has an extensive sympathetic innervation, may also contribute to the regulation of body weight.

Long term regulation of Appetite : The net effect of all the appetite-regulating mechanisms in normal adult animals and humans is an adjustment of food intake to the point where calorie intake balances energy expenditures, with the result that body weight is maintained. Children are notorious for their uneven food intake, their appetite for certain foods, and their unwillingness to eat others. However, over time they balance food intake with energy expenditure for immediate needs and growth and they grow and develop at a normal pace. Humans gain weight with advancing age, but this is normally a slow, carefully regulated process. One investigator calculated that the average woman gains 11 kg between the ages of 25 and 65. Considering that the total food intake of a woman over the 40 year period is more than 18 metric tons, the error in food intake over energy expenditure that produces the weight gain is less than 0.03%.

(Ref. Ganong 22th Edition; page 240)

Thirst

Thirst mechanism is under hypothalamic control. Drinking is regulated by plasma osmolality and ECF volume in much the same fashion as *vasopressin secretion*. Water intake is increased by increased effective osmotic pressure of the plasma, by decreases in ECF volume, and by psychologic and other factors. Osmolality acts via *osmoreceptors*, receptors that sense the osmolality of the body fluids. These osmoreceptors are located in the anterior hypothalamus.

Decreases in ECF volume also stimulate thirst by a pathway independent of that mediating thirst in response to increased plasma osniolality. Thus, *hemorrhage* causes increased drinking even though there is no change in the osmolality of the plasma. The effect of ECF volume depletion on thirst is mediated in part via the *renin-angiotensin system*. Renin secretion is increased by hypovolemia and results in an increase in circulating angiotensin II. The angiotensin II acts on the subfornical organ, a specialized receptor area in the diencephalon, to stimulate the neural areas concerned with thirst. There is some evidence that it acts on the organum vasculosum of the lamina terminalis (OVLT) as well. These areas are highly permeable and are two of the circumventricular organs located *outside the blood-brain barrier*. However, drugs which block the action of angiotensin II do not completely block the thirst response to hypovolemia, and it appears that the baroreceptors in the heart and blood vessels are also involved.

The intake of liquids is increased during eating (prandial drinking). The increase has been called a learned or habit response, but it has not been investigated in detail. One factor is any increase in plasma osmolality that occurs as the food is absorbed. Another may be an action of one or more gastrointestinal hormones directly on the subfornical organ. There is now some evidence that gastrointestinal hormones stimulate the same subfornical neurons that respond to angiotensin II.

Whenever the sensation of thirst is obtunded, either by direct

damage to the diencephalon or by depressed or altered states of consciousness, patients stop drinking adequate amounts of fluid. Dehydration results if appropriate measures are not instituted to maintain water balance. If the protein intake is high, the products of protein metabolism cause an osmotic diuresis, and the amounts of water required to maintain hydration are large. Most cases of *hypernatremia* are actually due to simple dehydration in patients with psychoses or cerebral disease who do not or cannot increase their water intake when their thirst mechanism is stimulated.

(Ref. Ganong 22th Edition; page 240)

Other factors-regulating water intake

A number of other well-established factors contribute to the regulation of water intake. Psychologic and social factors are important. Dryness of the pharyngeal mucous membrane causes a sensation of thirst. Patients in whom fluid intake must be restricted sometimes get appreciable relief of thirst by sucking ice chips or a wet cloth.

Some kind of pharyngeal gastrointestinal *metering* must be involved, though it is not well developed.

(Ref. Ganong 22th Edition; page 241)

Neural basis of instinctual behavior and emotions- *Limbic systems*

i. ***Introduction*** : Emotions have both mental and physical components. They involve *cognition*, an awareness of the sensation and usually its cause; *affect*, the feeling itself; *conation*, the urge to take action; and *physical changes* such as hypertension, tachycardia, and sweating.

The *hypothalamus* and *limbic systems* are intimately concerned with emotional expression and with the genesis of emotions.

ii. ***Anatomic considerations*** : The term *limbic lobe* or ***limbic system*** is applied to the part of the brain that consists of a rim of cortical tissue around the hilum of the cerebral hemisphere and a group of associated deep structures- amygdala, the hippocampus, and the septal nuclei. The region was formerly called the rhinencephalon because of its relation to olfaction, but only a small part of it is actually concerned with smell.

Histology : The limbic cortex is phylogenetically the oldest part of the cerebral cortex. Histologically, it is made up of-

a. *Allocortex* : a primitive type of cortical tissue, which in most regions has only three layers and surrounds the hilum of the hemisphere.

b. *Juxtallocortex* : A second ring of transitional cortex between the allocortex and the neocortex. It has three to six layers and is found in regions such as the cingulate gyrus and the insula.

The cortical tissue of the remaining nonlimbic portions of the hemisphere is called ***neocortex***. It generally has six layers and is the most highly developed type. The actual extent of the allocortical and juxtallocortical areas has changed little as mammals have evolved but these regions have been overshadowed by the immense growth of the neocortex, which reaches its greatest development in humans.

Correlations between structure & function : One characteristic of the limbic system is the paucity of the connections between it and the neocortex. However, from a functional point of view, neocortical activity does modify emotional behavior and vice versa. On the other hand, one of the characteristics of emotion is that it cannot be turned on and off at will.

Another characteristic of limbic circuits is their prolonged after-discharge following stimulation. This may explain in part the fact that emotional responses are generally prolonged rather than evanescent and outlast the stimuli that initiate them.

iii. ***Limbic functions*** :

a. Olfaction

b. The limbic system is concerned with autonomic responses, particularly changes in blood pressure and respiration.

c. Along with the hypothalamus, it is also concerned with-

1. Sexual behavior
2. Emotions of rage and fear
3. Motivation.

These responses are elicited from many limbic structures, and there is little evidence of localization of autonomic responses. This suggests that the autonomic effects are part of more complex phenomena, particularly emotional and behavioral responses.

(Ref. Ganong 22th Edition; page 256)

Sexual behavior

Mating is a basic but complex phenomenon in which many parts of the nervous system are involved. *Copulation* itself is made up of a series of reflexes integrated in spinal and lower brain stem centers, but the behavioral components that accompany it, the urge to copulate, and the coordinated sequence of events in the male and female that lead to *pregnancy* are regulated to a large degree in the limbic system and hypothalamus. Learning plays a part in the development of mating behavior, particularly in primates, but in nonprimate mammals, *courtship* and *successful mating* can occur with no previous sexual experience. The basic responses are therefore innate and are undoubtedly present in all mammals.

However, in humans, the sexual functions have become

extensively encephalized and conditioned by social and psychic factors.

i. ***Relation to endocrine function*** :

a. In nonprimate mammals, removal of the gonads leads eventually to decreased or absent sexual activity in both the male and the female-although the loss is slow to develop in the males of some species.

b. Injections of gonadal hormones in castrated animals revive sexual activity. Testosterone in the male and estrogen in the female have the most marked effect. Large doses of testosterone and other androgens in castrated females initiate female behavior, and large doses of estrogens in castrated males trigger male mating responses.

c. It is unsettled why responses appropriate to the sex of the animal occur when the hormones of the opposite sex are injected.

d. In women, *ovariectomy* does not necessarily reduce *libido* (defined in this context as sexual interest and drive) or sexual ability. Postmenopausal women continue to have sexual relations, often without much change in frequency from their premenopausal pattern. However, adrenal androgens are still present in these women.

e. Testosterone, for example, increases libido in males, and so does estrogen used to treat diseases such as carcinoma of the prostate. The behavioral pattern that was present before treatment is stimulated but not redirected. Thus, administration of testosterone to homosexuals intensifies their homosexual drive but does not convert it to a heterosexual drive.

ii. ***Neural control in the female*** : In mammals, the sexual activity of the female is cyclic. Most of the time, the female avoids the male and repulses his sexual advances. Periodically, however, there is an abrupt change in behavior and the female seeks out the male, attempting to mate. These short episodes of *heat* or *estrus* are so characteristic that the sexual cycle in mammalian species that do not menstruate is named the *estrous cycle.*

In women, sexual activity occurs throughout the menstrual cycle.

iii. ***Neural control in the male*** : In male animals, removal of the neocortex generally inhibits sexual behavior. However, cats and monkeys with bilateral limbic lesions localized to the piriform cortex overlying the amygdala develop a marked intensification of sexual activity. They not only mount adult females; they also mount immature females and other males and attempt to copulate with animals of other specics and with inanimate objects. The extent to which these animal studies are applicable to men are uncertain, though there have been a few reports of hypersexuality in men with bilateral amygdaloid lesions.

The hypothalamus also involved in the control of sexual activity in males. Simulation along the medial forebrain bundle and in neighboring hypothalamic areas causes penile erection with considerable emotional display in monkeys. In castrated rats, intrahypothalamic implants of testosterone restore the complete pattern of sexual behavior.

(Ref. Ganong 22th Edition; page 257, 258)

The reticular formation and the reticular activating system

The *reticular formation*, the phylogenetically old reticular core of the brain, occupies the midventral portion of the medulla and midbrain. It is primarily an anatomic area made up of various neural clusters and fibers with discrete functions. For example, it contains the cell bodies and fibers of many of the serotonergic, noradrenergic, and adrenergic systems. It also contains many of the areas concerned with regulation of heart rate, blood pressure, and respiration.

Some of the decending fibers in it inhibit transmission in sensory pathways in the spinal cord. Various reticular areas and the pathways from them are concerned with spasticity and adjustment of stretch reflexes.

The RAS is a complex polysynaptic pathway. Collaterals funnel into it not only from the long ascending sensory tracts but also from the trigeminal, auditory, and visual systems and the olfactory system. The complexity of the neuron net and the degree of convergence in it abolish modality specificity, and most reticular neurons are activated with equal facility by different sensory stimuli. The system is therefore *nonspecific*, whereas the classic sensory pathways are *specific* in that the fibers in them are activated by only one type of sensory stimulation. Part of the RAS bypasses the thalamus to project diffusely to the cortex. Another part ends in the intralaminar and related thalamic nuclei and, from them, is projected diffusely and nunspecificallv to the whole neocortex.

(Ref. Ganong 22th Edition; page 192)

Conciousness

A conscious person is awake and aware of himself or herself and the surroundings. For normal consciousness, active functioning of two main parts of the nervous system- the *reticulum formation* (in the brainstem) and the *cerebral cortex*- is necessary. The reticular formation is responsible for the state of wakefulness. The cerebral cortex is necessary for the state of awareness, that is, the state in which the individual can respond to stimuli and interact with the environment. *Eye opening* is a brainstem function: *speech* is a corearal cortex function. Drugs that produce unconsciousness, such as anesthetics, selectively depress the *reticular alerting mechanism*, while those that cause

wakefulness have a stimulating effect on this mechanism.

A physician should be able to recognize the different signs and symptoms associated with different stages of consciousness, namely, ***lethargy***, ***stupor***, and ***coma*** (*unconciousness*).

In a *lethargic individual* the speech is slow and the voluntary movement is diminished and slow. The movement of the eyes is slow.

A *stupored patient* will speak only stimulated with painful stimuli. The voluntary movements are nearly absent, the eyes are closed, and there is very litte spontaneous eye movement. A deeply stupored patient will not speak; there will be mass movements of different parts of the body in response to severe pain. The eyes will show even less spontaneous movement.

An unconscious patient will not speak and will respond only reflexly to painful stimuli, or not at all; the eyes are closed and do not move.

Clinically, it is not uncommon to observe a patient with, for example, intracranial bleeding pass progressively from conciousness to lethargy, stupor, and coma, and then, if recovery occurs, pass in the reverse direction. For these altered states of unconciouness to occur, the thalamocortical system and the reticular formation must be either directly involved bilaterally or indirectly affected by distortion or pressure.

(Clinical Neuroanatomy 5th Edition; page 295)

Sleep

Sleep is a changed state of consciousness.

Changes that occur in sleep :

i. Pulse rate decrease
ii. Respiratory rate decrease
iii. Blood pressure fall
iv. Eyes deviated upward
v. Pupils contract but react to light
vi. Tendon reflexes are lost
vii. Plantar reflex may become extensor.

A sleeping person is not, however, unconscious, because he or she may be awakened quickly by the cry of a child, for example, even though he or she has slept through the background noise of an air-conditioner.

Sleep is facilitated by reducing the sensory input and by fatigue. This results in decreased activity of the reticular formation and the thalamocortical activating mechanism. Whether this decreased activity is a passive phenomenon or whether the reticular formation is actively inhibited, is not known.

(Clinical Neuroanatomy 5th Edition; page 296)

Q. 00. **Describe how sleep and wakefulness are related to the reticular activating system (RAS).**

Ans. A sleeping person is not, however, unconscious, because he or she may be awakened quickly by the cry of a child, for example, even though he or she has slept through the background noise of an air-conditioner.

Sleep is facilitated by reducing the sensory input and by fatigue. This results in decreased activity of the reticular formation and the thalamocortical activating mechanism. Whether this decreased activity is a passive phenomenon or whether the reticular formation is actively inhibited, is not known.

(Clinical Neuroanatomy 5th Edition; page 296)

Q. 00. **How is non-REM sleep distinguished from rapid eye movement (REM) sleep?**

Ans. *Characteristics of non-REM sleep and REM sleep* :

non-REM	*REM sleep*
a. Originate in midline pontine and medullary nuclei raphe nuclei.	a. Originate in pontine reticular formation.
b. Mediated by serotonin	b. Mediated by noradrenaline.
c. Absence of eye movement	c. Rapid conjugate eye movement.
d. Stability of temperature, blood pressure, heart rate and respiration.	d. Fluctuation of temperature, blood pressure, heart rate and respiration.
e. Absence of muscle twisting.	e. Muscle twitchting present
f. Absence of dream.	f. Presence of dreams.

(Q. Mention the characteristics of rapid eye movement (REM) sleep.

Q. Mention the characteristics of non-REM sleep?

Q. Write short notes on- REKM).

Q. 00. **What is Bell-Magendie law?**

Ans. The principle that in the spinal cord the dorsal roots are sensory and the ventral roots are motor is known as the *Bell-Magendie law*.

(Ref Ganong 22th Edition, page-129)

Q. 00. **Write short notes on- Weber-Fechner law.**

Ans. Weber-Fechner law : There are two ways in which information about intensity of stimuli is transmitted to the brain by :

i. Variation in the frequency of the action potentials generated by the activity in a given receptor, and
ii. Variation in the number of receptors activated.

It has long been taught that the magnitude of the sensation felt is proportionate to the log of the intensity of the stimulus (Weber-Fechner law).

(Ref Ganong 22th Edition, page-126)

Cerebro-spinal fluid (CSF)

1. *Definition* : The fluid contained in the central canal of spinal cord, sub-arachnoid space and cerebral ventricles is known as CSF.
2. *Site of formation* : Most of the cerebrospinal fluid is elaborated by the *choroid plexuses* of lateral, third and fourth ventricles. A small amount of fluid is, however, formed by *diffusion from the brain* itself through the extra-choroidal, ependyma and from pial vessels.
3. *Rate of formation* : Average rate is about 20 ml/hour or 500 ml/day.
4. *Mechanism of formation* : Two theories :
   i. Filtration : Plays a minor role.
   ii. Secretion : This is the main process.
5. *Character* : It is a clear, colourless, transparent fluid, does not coagulate on standing & alkaline in reaction.

Specific gravity	:	1.004-1.006
Volume	:	About 150 ml in adults.
Pressure	:	110-130 mm of H_2O (1 drop/second thorugh lumber puncture needle).

6. *Composition* : CSF resembles colloid free plasma with certain variations of crystalloid content.
   a. *Water :* 99.13%
   b. *Solids :* 0.87%

i. Protein	:	20-30	mg%
ii. Glucose	:	50-80	mg%
iii. Chloride	:	700-750	mg%
iv. Cholesterole	:	0.06-0.22	mg%
v. Cells (leukocyte)	:	5	/cu. mm.
vi. Electrolytes	:	Na, K, Ca, Mg, HCO_3, urea, creatinine.	

7. *Function of C S F* :
   i. It acts as a fluid buffer.
   ii. It regulates the volume of cranial contents.
   iii. It is the medium through which nutritive materials as well as waste products are interchanged.

Formation of CSF

Most of the cerebrospinal fluid is elaborated by the *choroid plexuses* of lateral, third and fourth ventricles. A small amount of fluid is, however, formed by *diffusion from the brain* itself through the extra-choroidal, ependyma and from pial vessels.

Procedure : The rich vascular choroid plexuses present a surface area ranging from 150 to 300 sq.cm. The simple cuboidal epithelium of ependymal cells that line the choroidal villi (choroidal epithelium) are connected by tight junctions close to the apical portions of cells. Such tight junctions act as barriers and prevent the passage of proteins and other large molecules from the blood to the ventricular CSF. The CSF is mainly secreted by the choroidal epithelium by *active sodium pump* with expenditure of energy through the microvilli of the choroidal membrane. The net transfer of positive charge by the movement of Na^+ into the CSF is associated with the movement of Cl^- and HCO_3^- into, and the reciprocal movement of H^+ and K^+ out of the CSF. The movement of water into CSF takes place passively to maintain osmotic equilibrium. Thus, the choroidal epithelium acts bi-directionally and is specialised to secrete, to dialyse and to absorb. As the cerebrospinal fluid circulates, its composition is further modified by exchanges of solutes with the brain across the ventricular ependyma and with the plasma across the pia-arachnoid of the subarachnoid space.

Circulation of CSF

After its formation by the choroid plexuses of the lateral ventricles, the fluid appears in the third ventricle through the two interventricular forarnina, and thence into the fourth ventricle through the *aqueduct of Sylvius*. From the fourth ventricle the CSF leaves the ventricular system and enters into the cerebello-medullary cisern through the foramen of *Magendie* and foramina of *Luschka* in the roof of the fourth ventricle.

Thereafter, the CSF circulates in two directions :

a. A part of the fluid undergoes sluggish movement caudally along the spinal subarachnoid space, depending in part upon the movement of the vertebral column.
b. The bulk flow of the fluid from the cerebellomedullary cistern, however, takes place in rostral direction through the tentorial notch. The fluid passes sucessively along the inferior surface and the supero-lateral surface of the cerebral hemisphere until the fluid reaches the arachnoid villi associated with the superior sagital sinus for its final absorption into the venous blood.

Absorption of CSF

Most of the fluid is drained into the venous blood of the superior sagittal sinus through the arachnoid granulations which are composed of numerous arachnoid villi. The arachnoid villi are permeated by a network of minute channels (vide supra) which act as one-way valves and permit bulk flow of the CSF including macromolecules of proteins from the subarachnoid space to the dural venous sinus, preventing at the same time the reverse flow. Such unidirectional flow is regulated by the pressure CSF. Higher colloid osmotic pressure of the venous blood may facilitate the absorption of CSF. A small amount of the fluid may be absorbed into the cervical lymphatics along the sheaths of the cranial nerves.

Thus, the cycles of formation., circulation and absorption of CSF follow a pressure gradient from the high pressure capillary bed of choroid plexuses to the low pressure fluid-filled ventricles and subarachnoid space, and thence to the lowest pressure of the venous blood of the dural sinus (Noback).

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Directions Write rue& 'F' for false against each of the following statement.

Introduction

Q. 01. **Brain stem consists of**
- T a. mid brain
- T b. medulla oblongata
- T c. pons
- F d. fore brain
- F e. hind brain.

Q. 02. **Nervous system**
- T a. is the unique system of thought and control action
- T b. receives information
- T c. integrates all the information
- T d. consists of sensory division
- F e. is the only control system of the body.

Q. 03. **The nervous system controls**
- T c. the rapid activities of the body
- T b. the rate of secretion of some endocrine glands
- T d. the rapidly changing visceral events
- T e. the muscle contraction.
- F a. the metabolic activities of the body

Q. 04. **In the postnatal period the greatest growth in the grey matter of the CNS is of**
- T a. Dendritic tree
- F b. Neuron cell number
- F c. Length of axon
- F d. Size of Perikaryon
- F e. Length of nerve fiber.

Q. 05. **phagocyttosis in the CNS is done by**
- T a. Microglia
- F b. Astrocytes
- F c. Schwann cells
- F d. Oligocytes
- F e. Macverophages.

Q. 06. **Blood brain barrier is deficient at**
- T a. Area postrema
- F b. Thalamus
- F c. Meta thalamus
- F d. Cerebellum
- F b. Hypothalamus.

Q. 07. **Blood brain barrier is made up of**
- T a. Astrocytes
- F b. Oligodendrocytes
- F c. Oligodendroglia
- F d. Microglia
- F e. Schwann cells.

Q. 08. **The blood brain barrier**
- T a. slows equilibration of solutes between blood & brain tissue fluid.
- T b. is highly permeable to water
- F c. is more effective barrier for fat soluble substances than water soluble substance
- F d. is highly permeable to plasma protein
- F e. is more effective barrier in infants than in adults.

Q. 09. **The blood brain barrier**
- T a. permits CO_2 to pass easily
- T b. is more permeable in infants than in adults
- T c. allows bilirubin to cross in infants.
- F d. is more permeant to water soluble substances
- F e. permits H^+ to pass freely

Q. 10. **Regarding brain metabolism**
- T a. it accounts for about 15% of the total metabolism in the body
- T b. per unit mass of tissue is about 7.5 times the metabolism in non nervous tissue
- T c. it occurs in the neutrons
- F d. it accounts for about 50% of the total body metabolism
- F e. it occurs in glial supportive tissue.

Q. 11. **Oxygen consumption of whole human brain in ml/minute is about**
- T a. 49
- F b. 29

F c. 35
F d. 6
F e. 40.

Q. 12. **Repolarization state of the action potential includes**
T a. essential diffusion of K^+ ions outward through the membrane
T b. return of membrane potential to the resting level.
F c. important action of Na^+-K^+ pump
F d. increase in Na^+ conductance to 20 times its normal.
F e. no change in K^+ conductance.

Q. 13. **The motor function are**
T a. contraction of skeletal muscles
T b. contraction of smooth muscles in the internal organs
T c. secretion by exocrine glands
F d. activation of intracellular enzymes
F e. intracellular protein synthesis.

Q. 14. **Skilled motor function is**
T a. dependent on pyramidal system
T b. largely influenced by slowly acting feedback from proprioceptors.
T c. dependent on visual feedback
F d. initiated only in the cerebral cortex
F e. greatly affected by transection of extrapyramidal tracts.

Spinal cord

Q. 15. **Spinal cord**
T a. receives sensory signal through posterior root
T b. has alpha motor neuron
T c. has gamma motor reuron.
F d. receives sensory signal through anterior root
F e. has delta motor neuron

Q. 16. **phagocyttosis in the CNS is done by**
T a. Microglia
F b. Astrocytes
F c. Schwann cells
F d. Oligocytes
F d. Macrophages.

Q. 17. **Lowest most level of integration of stretch reflex is at**
T a. Spinal cord
F b. Cerebral cortex
F c. Medulla
F d. Lower medulla
F e. All of the above.

Q. 18. **Inhibition of the spinal cord may be brought about by**
T a. Glycine
F b. Glutamic acid
F c. Aspartic acid
F d. Strychiniae
F e. None of the above.

Q. 19. **Which of the following reflexes disappear in the absence of functional connections between the spinal cord and the brain?**
T a. Swallowing reflex
F b. Seating reflex
F c. Withdrawal reflex
F d. Erection of penis
F e. All of the above

Q. 20. **Hemisection of the spinal cord at cervical level causes**
T a. loss of motor activity in same side
T b. no loss of micturation reflex
F c. loss of pain sensation in same side
F d. greater loss of conscious proprioception in the opposite side
F e. respiratory failure

Q. 21. **If we divide the spinal cord above medulla, what happens to respiration?**
T a. Normal respiration.
F b. It becomes slower and deeper
F c. Apneustic breathing
F d. Breathing ceases
F e. Abormal respiration.

Q. 22. **Autonomic segmental reflexes occurring in the spinal cord are**
T a. emptying reflexes of the urinary bladder
T b. sweating
T c. vascular response to heat and cold
F d. dynamic stretch reflex
F e. papillary reflex

Q. 23. **Neuronal circuits in spinal cord cause**
T a. walking movement
T b. reflexes that withdraw body from painful object
T c. reflex that control blood vessels
F d. reflex that attract body towards painful object
F d. steady state condition.

Q. 24. **Below the level of spinal hemisection supports the following features**
T a. extensive sensory loss on opposite side
T b. extensive motor loss on same side
T c. little motor loss on opposite side
F d. extensive motor loss on opposite side
F e. extensive sensory loss on same side

CSF

Q. 25. **CSF is principally secreted by**

T a. Choroid plexus
F b. Arachnoid granulation
F c. Floor of fourth ventricle
F d. Periaqueductal grey
F e. 1 ml/min.

Q. 26. **CSF production per minute**
T a. 0.30 - 0.35 ml/min
F b. 0.5 ml/min
F c. 2 ml/min
F d. 1 ml/min
F e. 1 L/min

Q. 27. **CSF pressure (lumbar)**
T a. 70 - 180 mm CSF
F b. 50 - 100 mm CSF
F c. > 200 mm CSF
F d. 150 - 200 mm CSF
F d. 90 - 120 mm CSF.

Q. 28. **CSF pressure in the lying down posture is**
T a. 50-150 mm of Hg
F b. 20-50 mm of Hg
F c. 150-200 mm of Hg
F d. 200-300 mm of Hg
F d. 40-70 mm of Hg.

Q. 29. **Below..... pressure CSF absorption stops**
T a. 68 mm CSF
F b. 60 mm CSF
F c. 80 mm CSF
F d. 50 mm CSF
F d. 95 mm CSF.

Q. 30. **CSF in comparison to blood contains**
T a. Lower calcium
T b. Lower sodium
T c. Lower cells
F d. Lower chloride
F e. Lower macrophages.

Q. 31. **Cerebrospinal fluid**
T a. is secreted by choroid plexus
T b. is absorbed by arachnoidal villi.
T c. has got same osmotic pressure as plasma
F d. is formed at a rate of 100 ml/day
F e. has got same concentration of glucose as plasma.

Q. 32. **Regarding cerebrospinal fluid**
T a. it fills the subarachnoid space
T b. the rate of production is about 550 ml/day
T c. it is produced by choroid plexus.
F d. the composition differ from brain extracellular fluid.
F e. it does not protect the brain.

Q. 33. **P^{H} of CSF is**
T a. 7.33
F b. 7.13
F c. 7.23
F d. 7.40
F e. 7.38

Q. 34. **Volume of CSF is about**
T a. 150 ml
F b. 50 ml
F c. 100 ml
F d. 200 ml
F e. 250 ml.

Q. 35. **CSF does not pass through**
T a. Epidural spaces
F b. Ventricles
F c. Venous sinuses
F d. Subarachnoid space
F e. 4th cventricles.

Q. 36. **All the following are more in CSF compared to plasma except**
T a. Glucose
F b. Mg
F c. Cl
F d. HCO_3
F e. All of the above.

Q. 37. **True statement regarding CSF is**
T a. It flows fromIII ventricle to the IV ventricle
T b. Produced mainly by choroid plexus.
F c. Produced only by choroid plexus.
F d. Daily production < 700 ml
F e. CSF analysis rules out active secretion as a cause of formation of CSF

Q. 38. **Indications of lumbar puncture**
T a. to obtain CSF sample
T b. to inject diagnostic agent
F c. elevated intracranial pressure
F d. severe degenerative joint disease
F e. coagulation abnormalities.

Autonomic nervous system

Q. 39. **Autonomic nervous system controls**
T a. contraction of smooth muscle
T b. relaxation of cardiac muscle
T c. secretion of gland
T d. different internal bodily system.
F e. contraction and relaxation of skeletal muscles

Q. 40. **Sympathetic nervous system stimulation causes**
T a. increased arterial pressure

T b. increased mental activity.
T c. increased blood glucose concentration
F d. decreased muscle strength
F e. decreased rate of blood coagulation

Q. 41. **Sympathetic stimulation cause**
T a. increased heart rate
T b. dilatation of bronchi.
T c. dilatation of the pupil
F d. constriction of the pupil
F e. decreased heart rate

Q. 42. **Sympathetic stimulation causes**
T a. glycogenolysis
T b. increased sweat secretion.
F c. bronchial muscle contraction
F d. papillary constriction
F e. skeletal muscle vasoconstriction

Q. 43. **Stress response of sympathetic nervous system are**
T a. increased blood pressure
T b. increased glycolysis
T c. increased rate of blood coagulation.
F d. decreased blood glucose concentration
F e. decreased muscle strength

Q. 44. **Sympathomimetic drugs are**
T a. also called adrenergic drugs
T b. epinephrine and nor epinephrine
T c. act by stimulating sympathetic nerve
F d. also called cholinergic drugs
F e. acetylcholine and pilocarpine

Q. 45. **Parasympathetic nerves**
T a. if stimulated cause papillary constriction
T b. have preganglionic fibers longer than those of post ganglionic
F c. if stimulated cause decreased peristalsis and tone of the gut lumen
F d. When stimulated causes copious sweating
F e. cause vasodilation in skin

Q. 46. **Parasympathetic stimulation causes**
T a. constriction of pupil
T b. constriction of bronchi
T c. contraction of gall bladder
F d. increased heart rate
F e. increased force of contraction of heart muscle.

Q. 47. **Parasympathomimetic drugs**
T a. are also called cholinergic drugs
T b. act by stimulating parasympathetic nerve
T c. are acetylcholine and pilocarpine
F d. act by inhibiting parasympathetic nerve
F e. are epinephrine and norepinephrine.

Q. 48. **Autonomic ganglion is mainly**
T a. Cholinergic
F b. Adrenergic
F c. Dopamergic
F d. Serotonergic
F e. All of the above.

Q. 49. **Vagal stimulation causes the following effects**
T a. Intestinal secretion
T b. Consticton of intestinal musculature
T d. Fall in blood pressure
F c. Relaxation of bronchial musculature
F e. All of the above.

Q. 50. **Right and left vagus respectively go to:**
T a. SA node, AV node
F b. AV node, SA node
F c. AV node, bundle of His
F d. SA node, bundle of His
F e. Inter nodal pathway.

Q. 51. **Bathmotropic effect is produced by**
T a. Stimulation of vagus
F b. Nerves other than vagus
F c. Atropine
F d. Section of vagus
F e. Homatropin.

Q. 52. **Gag reflex is mediated by cranial nerve**
T a. IX
F b. VII
F c. X
F d. XII
F e. II

Neuron

Q. 53. **In a neuron**
T a. axon is the motor part
T b. dendrite is the sensory part
F c. axon is the sensory part
F d dendrite is the motor part
F e soma is the motor part.

Q. 54. **A neuron**
T a. is the structural and functional unit of nervous system
T b. transmit impulses from one part of the body to another
T c. contains dendrite and axon
F d. has no nucleus
F e. has ability for division.

Q. 55. **Internuncial neurons are**
F a. Essential part of stretch reflex

F b. Essential part of all reflexes
F c. Always excitatory
F d. Always inhibitory
T e. None of the above

Q. 56. **Neuronal soma contains more**
T b. more Na^+ ion outside
T c. more K^+ ion inside
T e. less Cl^- ion inside.
F d. more K^+ ion outside
F a. ion inside

Q. 57. **What is true regarding the gamma efferent neuron?**
T a. An *A group motor neuron* with a smaller diameter than that of alpha etferent neurons
T b. Innervates intrafusal fibres
T c. Innervates muscle fibres that stretch annulospiral endings
T d. All of the above
F d. None of the above.

Q. 58. **Increased Gamma efferent discharge is seen in**
T a. Jendrassik's maneuvre
T b. Anxiety
T c. Stimulation of skin
F d. Rapid shallow breathing
F er. Rapid heraert breat.

Q. 59. **Dendrite**
T a. are branching processes
T b. extend from soma
T c. contain presynaptic terminals
F d. are non-branching processes
F e. extend from axon

Q. 60. **An axon**
T a. is single in number.
T b. conducts impulses away from the cell body
T c. is the beginner of action potential by EPSP
F d. conducts impulses away from CONS
F e. is poor in voltage gated Na^+ channel

Q. 61. **Non myelinated axons differ from myelinated in that they**
T a. Lack nodes of Ranvier
F b. Are more excitable
F c. Are not capable of regeneration
F d. Are not capable of dfegeneration
F e. Are not associated with Schwann cells

Q. 62. **Changes in nerve cell body due to degeneration are**
T a. broken up golgi apparatus.
T b. chromatolysis
T c. nucleus pushed to the periphery
F d. nucleus pushed to the centre
F e. shrinking of cell

Q. 63. **The action potential of a neuron**
T a. is associated with net movement of Na^+-K^+ across the membrane
T b. is initiated by rapid influx of Na^+
F c. is maintained by slow influx of Ca^{++}
F d. shows plataue potential before repolarization
F e. lasts more than that of cardiac muscle.

Q. 64. **Effects of upper motor neuron lesion are**
T a. loss of superficial reflex
T b. Spastic paralysis
F c. muscle wasting
F d. loss of deep reflex
F e. decrease muscle tone.

Q. 65. **Upper motor neuron lesion produces**
T a. hyper-reflexia
T b. disuse atrophy of the muscle
F c. flaccid paralysis
F d. extensive sensory loss
F e. plantar flexion.

Q. 66. **A unilateral upper motor neuron lesion in the internal capsule is best characterized by**
T a. Diminished use of contralateral appendages below the lesion
F b. Rapid shallow breathing
F c. Ipsilateral hypotonicity
F d. Flexion of the leg
F e. Rapid shallow breathing.

Q.67. **Lower motor neuron lesion produces**
T a. flaccid paralysis
T b. atrophy of the muscle
T c. hyper-reflexia.
F d. extensor plantar response
F e. fasciculation

Q. 68. **Neuronal activity is**
T a. increased by theophyline
T b. increased by caffeine
T c. decreased by glycine.
F d. inhibited by caffeine
F e. decreased by theophyline

Nerve fibre

Q. 69. **Group B fibre are**
T a. Sympathetic preganglionic
T b. Parasympathetic preganglionic
F c. Sympathetic post ganglionic
F d. Parasympathetic post ganglionic
F e. All of the abocve.

Q. 70. **Wallenberg degeneration is seen in**
- T a. Proximal cut end of nerve with cell body
- F b. Distal cut end of nerve without cell body
- F c. Both the free ends of the cut nerve
- F d. Only the cell body
- F d. All are true.

Q. 71. **First change to occur after nerve cut is**
- T a. Myelin sheath degeneration
- F b. Schwan cell mitosis
- F c. Axonal sprouting
- F d. Myelin sheath regeneration
- F e. Nuclear disintegration

Q. 72. **Which of the following nerve fibres is affected by local anaesthetics first**
- T a. C
- F b. Type II
- F c. A
- F d. B
- F e. Aβ.

Q. 73. **What are some of the modalities of sensation that are detected by free nerve endings?**
- T a. Crude touch
- T b. Pain
- T c. Tickle snesations
- F d. Muscle stretch
- F e. Isometric contraction

Q. 74. **The purkinje fibres**
- T a. Have a conduction velocity of about fives time that seen in head muscle
- F b. Have action potentials about a tenth as long as those in heart muscle
- F c. Are myelinated axons
- F d. All of the above
- F e. None of the above.

Q. 75. **Spike duration is maximum in which nerve fibre :**
- T a. A-beta
- F b. A-alpha
- F c. A -delta
- F d. C
- F e. B.

Q. 76. **The percentage of pyramidal fibres which are unmyelinated**
- T a. 50
- F b. 20
- F c. 35
- F d. 75
- F e. 65

Q. 77. **The most susceptible fibre to hypoxia is**
- T a. B
- F b. A
- d c. C
- e d. Aδ
- F e. All are equally sensitive

Q. 78. **First change to occur in the distal segment of cut nerves**
- T a. Axonal degeneration
- F b. Myelin degeneration
- F c. Mitosis of schwann cell
- F d. Myelin regeneration
- F e. Axonal regeneration

Q. 79. **The fibre which is the thickest in human nerve is**
- T a. Proprioception
- F b. Touch
- F c. Pain
- F d. Temperature
- F e. Hot.

Q. 80. **Conduction in which type of nerve fibres is blocked maximally by pressure?**
- T a. A-beta
- F b. C
- F c. A-alpha
- F d. A-gamma
- F e. B.

Q. 81. **Percentage of sensory fibres in a pure motor nerve is**
- T a. 40 %
- F b. 0 %
- F c. 10 %
- F d. 2 %
- F e. 25 %

Q. 82. **Relation between nerve thickness and conduction velocity is**
- T a. Linear
- F b. Parabolic
- F c. Hyperbolic
- F d. No relation
- F e. All of the above.

Q. 83. **The intensity of sensory stimuli is determined by**
- T a. Frequency of action potential
- F b. Duration of latent period
- F c. Amplitude of action potential
- F d. Amplitude of generation potential
- F e. All of the above.

Q. 84. **Which is true about resting membrane potential of the nerve**
- T a. Potassium (extracellular) mainly
- F b. Can be measured by applying electrode over the nerve fibre contributes

F c. Equal to the resting membrane potential of the muscle.
F d. Reduction of RMP Inhibits a voltage dependent increase in sodium ion permeability
F e. None of the above.

Q. 85. **Which sensation is not lost on the side of lesion in Brown sequard syndrome**
T a. Temperature
F b. Touch
F c. Vibration sense
F d. Muscle sense
F e. None of the above.

Q. 86. **The myelin sheath**
T a. is interrupted by nodes of Ranvier
T b. provides saltatory conduction
F c. significantly decreases conduction velocity
F d. is found on C-fibers
F e. of the axons in central nervous system, is formed by schwann cells.

Q. 87. **The velocity of conduction of nerve nerve fibers is**
T a. increased with increase in fiber diameter
T b. as high as 130 meters/second
F c. decreased with increase in fiber diameter
F d. not related to diameter of the fiber
F e. faster in unmyelinated than in myelinated nerve fibers.

Q. 88. **C-fibers**
T a. conduct impulse at low velocity
T b. conduct pain sensation
F c. are myelinated nerve fibers
F d. possess saltatory nerve conduction
F e. conduct position sensation.

Q. 89. **Wallerian degeneration is characterized by**
T a. mitotic division of schwann cells
T b. invasion by microglial cells
T c. breaking of myelin sheath into fat droplets.
F d. chromatolysis
F e. dissolution of nissl granules

Q. 90. **Conductivity & excitability of a nerve fibre increases due to**
T a. increased temperature
T b. Na^+-K^+ (neuroexcitatory)
F c. mechanical pressure
F d. CO_2
F e. Ca^{++} (neuroselective).

Q. 91. **General classification of nerve fiber are**
T a. Aα
T b. Aγ
T c. C
F d. D
F e. E

Q. 92. **Properties of nerve fibers are**
T a. excitability
T b. conductivity
T c. refractory period.
F d. autorhythmicity
F e. contractility

Q. 93. **Myelinated nerve fibers are**
T a. type A fibers
T b. group III
T c. type Aδ fibers
F d. type C fibers
F e. group IV.

Q. 94. **Unmyelinated nerve fiber**
T a. constitutes more than one half in most peripheral sensory fibers.
T b. constitutes all of the post ganglionic fibers
F c. are Aα fibers
F d. conducts impulese at high velocity
F e. has diameter ranging from 1 to 20 micrometer.

Q. 95. **Unmyelinated nerve fibers are**
T a. type C fiber
T b. group IV fiber
F c. group II fiber
F d. type A fiber
F e. type B fiber

Q. 96. **Stimulation of vagus nerve causes**
T a. mucous secretion from bronchial mucosal cell
T b. contraction of gall bladder
F c. contraction of spleen
F d. secretion in the the salivary gland
F e. reduction in the strength of ventricular contraction.

Receptor

Q. 97. **Receptor which itself is a dendrite of a nerve**
T a. Olfactory
F b. Gustatory
F c. Visual
F d. Hearing
F e. All of the above.

Q. 98. **Paccinian corpuscles are major receptors for**
T a. Pressure
F b. Pain
F c. Touch
F d. Temperature
F e. All of the above.

Q. 99. **Which is caused by acetylcholine through nicotinic receptors**
- T a. Contraction of skeletal muscle
- F b. Descrease of heart rate
- F c. Secretion of saliva
- F d. Contraction of pupils
- F e. All of the above.

Q. 100. **Stimulants that cause excitation of receptors are**
- T a. mechanical deformation of receptors
- T b. application of chemicals to the membrane
- T c. changes of temperature of the membrane
- T d. effect of electromagnetic radiation on the receptor.
- F e. application of toxic substance to the membrane

Q. 101. **Slowly adapting receptors are**
- T a. receptors in the vestibular apparatus
- T b. pain receptors
- T c. baroreceptors
- T d. chemoreceptor.
- F e. thermoreceptors

Q. 102. **Mechanoreeeptors are**
- T a. free nerve endings
- T b. muscle spindles
- T c. golgi tendons
- F d. cold receptors
- F e. rods.

Q. 103. **Electromagnetic receptors**
- T a. are rods
- T b. are cones
- T c. detect light on retina
- F d. detect osmolality of body fluid
- F e. are present in vessel wall.

Q. 104. **Sensory receptors**
- T a. adapt partially
- T b. adapt completely
- T c. respond at a high impulse rate at first
- F d. respond at a low impulse rate at first
- F e. respond progressively at higher rate.

Q. 105. **Meissner's corpuscle found in**
- T a. finger tip
- T b. lips
- F c. joint capsule
- F d. deep facial tissue
- F e. hairy part of skin.

Q. 106. **Free nerve endings are present in**
- T a. joint surface
- T b. periosteum
- T c. arterial wall
- F d. retinal wall
- F e. wall of GIT.

Q. 107. **Pacinian corpuscles are**
- T a. rapidly adapting touch receptors
- T b. mechanoreceptors
- T c. adapted due to readjustments in the structures of the receptor itself
- F d. responsive to pain stimulation
- F e. types of temperature receptor

Q. 108. **Sensory receptors**
- T a. undergo rapid and slow adaptation.
- T b. act as transducers to produce receptor potential
- T c. are highly sensitive to one type of stimulus
- F d. show propagated type of action potential.
- F e. are specialized to respond to different forms of energy.

Q. 109. **The mechanoreceptors are**
- T a. merkel's disc
- T b. krause's corpuscles
- T c. muscle spindle.
- F d. receptors of taste bud
- F e. rods and cones

Q. 110. **Receptor for**
- T a. vision are rods and cones
- T b. pressure are pacinian corpuscles
- F c. proprioception are free nerve ending
- F d. temperature are nociceptors
- F e. pain sensation are stretch receptors.

Q. 111. **α -receptors cause**
- T a. vasoconstriction
- T b. iris dilatation
- T c. intestinal sphincter contraction
- F d. vasodilatation
- F e. intestinal sphincter relaxation.

Q. 112. **Beta receptors cause**
- T a. cardioacceleration
- T b. bronchodilatation
- T c. vasodilatation
- F d. vasoconstriction
- F e. bronchoconstriction.

Q. 113. **The following are the few examples of sensory receptors with their sense organs**
- T a. rods and cones : eye
- T b. baroreceptor : aortic arch
- F c. hair cells : olfactory epithelium
- F d. muscle spindles : tendon of the muscle
- F e. salty taste buds : posterior part of the tongue.

Q. 114. **The following are the sensory receptors with their respective sensations**
- T a. olfactory epithelium : smell
- T b. baroreceptors : blood pressure.
- T c. free nerve endings : pain
- F d. pacinian corpuscles : cold sensation
- F e. osmoreceptor : blood PCO_2

Neurotransmitters

Q. 115. **Receptor which itself is a dendrite of a nerve**
- T a. Olfactory
- F b. Gustatory
- F c. Visual
- F d. Hearing
- F e. All of the above.

Q. 116. **Paccinian corpuscles are major receptors for**
- T a. Pressure
- F b. Pain
- F c. Touch
- F d. Temperature
- F e. All of the above.

Q. 117. **Which is caused by acetylcholine through nicotinic receptors**
- T a. Contraction of skeletal muscle
- F b. Descrease of heart rate
- F c. Secretion of saliva
- F d. Contraction of pupils
- F e. All of the above.

Q. 118. **Alpha component of G protein act by**
- T a. activation of gene transcription
- T b. opening specific ion channel
- T c. activation of enzyme
- F d. inactivation of enzyme
- F e. inactivation of gene transcription.

Q. 119. **Acetylcholine**
- T a. is synthesized from acetic acid
- T b. releases from all post ganglionic parasympathetic neuron
- T c is destroyed by acetyl cholinesterase
- F d. acts as inhibitory neurotransmitter
- F e. releases from all post ganglionic sympathetic neuron

Q. 120. **Norepinephrine is**
- T a. secreted from adrenal medulla
- T b. synthesized from tyrosine
- T c. destructed by monoamino-oxidase
- F d. destructed in spleen
- F e. the parasympathetic transmitter.

Q. 121. **Of the neurotransmitter**
- T a. serotonin is the sleep inducing neurotransmitter.
- T b. dopamine is rapidly acting transmitter
- T c. gastrin acts on brain
- F d. GABA is slowly acting transmitter
- F e. glutamate always cause inhibition

Q. 122. **The following neurotransmitter are peptides**
- T a. substance-P
- T b. met-enkephalin
- T c. β-endorphin
- F d. serotonin
- F e. acetylcholine.

Q. 123. **The following neurotransmitter are synthesized in the preganglionic sympathetic neutrons**
- T a. norepinephrine
- T b. acetylcholine
- T c. L-Dopa
- F d. histamine
- F e. glutamine.

Q. 124. **The following are the few examples of excitatory and rapidly acting neurotransmitter**
- T a. nitric oxide
- T b. epinephrine
- F c. GABA
- F d. dopamine
- F e. substance P

Q. 125. **Acetylcholine is secreted at the endings of**
- T a. preganglionic fibers to the adrenal medulla
- T b. motor nerves at the myoneural junction.
- T c. preganglionic sympathetic
- T d. preganglionic parasympathetic
- F e. preganglionic sympathetic fibers supplying skin blood vessels

Q. 126. **IPSP produced by the neurotransmitter are**
- T a. GABA
- T b. dopamine
- T c. glycine
- F d. adrenaline
- F e. acetylcholine.

Q. 127. **Rapidly acting neurotransmitter are**
- T a. glutamate
- T b. glycine
- F c. gastrin
- F d. cholecystokinin
- F e. angiotensin II.

Q. 128. **Slowly acting neurotransmitter are**
- T a. thyrotropin
- T b. cholecystokinin
- F c. dopamine

F d. histacine
F e. serotonin.

Q. 129. **Neurotransmitter acting on basal ganglia are**
T a. norepinephrine.
T b. dopamine
T v. acehylcholine
T d. gamma aminobutyric acid
F e. epinephrine

Q. 130. **Neuropeptides**
T a. are produced in endoplasmic reticulum
T b. are more potent than small molecule transmitters
T c. usually cause prolonged actions
F d. are removed within milli-seconds
F e. are GABA, nitric oxide, dopamine etc.

Synapse

Q. 131. **IPSP is due to**
T a. Cl^- influx
F b. K^+ influx
F c. Na^+ influx
F d. Ca^{++} influx
F e. Mg^{++}.

Q. 132. **EPSP is due to**
T a. Na^+ influx
F b. K^+ influx
F c. Na^+ eflux
F d. Ca^{++} influx
F e. Mg^{++}.

Q. 133. **Synapse**
T a. determines the direction of nervous signals
T b. is the junction of two neutrons
T c. in CONS are almost chemical in nature
F d. in CONS are almost electrical in nature
F e. blocks strong signal but allows weak signal to pass.

Q. 134. **Chemical synapse**
T a. acts by releasing neurotransmitter
T b. transmits signals in one direction
T c. is mainly present in CNS
F d. transmits signals in both direction
F e. is mainly present in PNS.

Q. 135. **A chemical synapse exhibits following properties**
T a. delay
T b. summation
T c. presynaptic inhibition
F d. two way conduction
F e. infatigability

Q. 136. **Presynaptic terminals**
T a. contain mitochondria.
T b. are called synaptic knob
T c. are separated from post synaptic terminal by synaptic cleft
T d. contain transmitter substance
F e. contain no mitochondria

Q. 137. **Presynaptic membrane contains**
T a. release site
T b. voltage gated calcium channel
F c. no calcium channel
F d. sodium channel
F e. no release site.

Q. 138. **Post synaptic membrane contains**
T a. excitatory receptors.
T b. cation channel
T c. anion channel
F d. no anion channel
F e. no cation channel.

Q. 139. **Excitatory post synaptic potential (EPSP) are due to**
T a. depression of K^+ channel
T b. opening of Na^+ channel
F c. opening of Cl^- channel
F d. opening of K^+ channel
F e. increased conduction through Cl^- channel

Q. 140. **Inhibitory post synaptic potential (IPSP) are due to**
T a. increased conductance of K^+
T b. activation of receptor enzyme.
T c. opening of $C1^-$ channel
F d. closing of $C1^-$ channel
F f. opening of Na^+ channel

Q. 141. **Excitatory post synaptic potential is due to**
T a. depressed conduction through chloride channel
T b. decreased conductance of K^+ channel
T c. opening of Na^+ channels
F d. opening of chloride ion (Cl^-) channel
F e. increased conductance of K^+ channel.

Q. 142. **Synaptic transmission**
T a. is decreased in acidosis.
T b. become fatigue due to repetitive stimulation
T c. is increased in alkalosis
F d. become over stimulated due to repetitive stimulation
F e. is decreased in alkalosis

Q. 143. **Transmission of impulse across a chemical synapse needs**
T a. spreading of action potential over a presynaptic terminal

T b. activation of post-synaptic ion channel by neurotransmitter
T c. activation of second messenger systems within the neuron.
F d. Ca^{++} influx through the post-synaptic neuron to release neurotransmitter.
F e. release of excitatory neurotransmitter only.

Q. 144. **Excitation of the post-synaptic neuron occurs by**
T a. decreasing Cl^- influx
T b. activation of Na^+ channels
F c. opening of anion channels
F d. releasing GABA from pre-synaptic terminal.
F e. increasing the K^+ conductance to the exterior.

Q. 145. **Some post synaptic receptors, when activated cause excitation of the post synaptic neuron by**
T a. an increase in the number of excitatory membrane receptors.
T b. opening of sodium channels
F c. opening of calcuim channels
F d. opening of chloride channels
F e. an increase in the conductance of potassium ions through the receptor

Q. 146. **Saltatory conduction**
T a. conserves energy for the axon because only the nodes depolarize.
T b. is faster than nonsaltatory conduction
T c. transmits impulses with a velocity proportional to fibre diameter
F d. is accomplished almost entirely by the sequential changes in the voltage gated potassium channel
F e. occurs only in unmyelinated nerve fibers

Reflex

Q. 147. **Crossed extensor reflex is a**
T a. Withdrawal reflex
F b. Postural reflex
F c. Monosynaptic reflex
F d. Sympathetic reflex
F e. parasympathetic reflex.

Q. 148. **All these are seen in a spinal reflex**
T a. Summation
T c. Memory
T d. Adaptation
F b. Fatigue
F e. All of the above.

Q. 149. **Unidirectional transport is seen across**
T a. Synapse
F b. Axon
F c. Both of above
F d. None of above
F e. All of the above.

Q. 150. **Lowest most level of integration of stretch reflex is at**
T a. Spinal cord
F b. Cerebral cortex
F c. Medulla
F d. Lower medulla
T e. Pons.

Q. 151. **Superficial reflexes are**
T a. Corneal
T b. Plantar
F c. Ankle
F d. Hoffmans
F e. Jaw

Q. 152. **The basic postural reflex is**
T a. Flexor reflex
F b. Crossed extensor reflex
F c. Golgi tendo reflex
F d. Positive supporting reflex
F e. Jaw.

Q. 153. **A reflex action**
T a. is initiated at a sensory receptor organ
T b. may result in endocrine secretion
T c. is excitatory
T d. is inhibitory.
F e. is independent of higher centers in the brain

'Q. 154. **Superficial reflexes are**
T a. papillary reflex
T b. plantar reflex
T c. cremasteric reflex
F d. knee jerk
F e. ankle jerk.

Q. 155. **Deep reflexes are**
T a. biceps jerk
T b. ankle jerk
T c. knee jerk
F d. papillary reflex
F e. conjunctival reflex.

Q. 156. **Reflex arc**
T a. has afferent nerve fibers
T b. has receptor
T c. is a complete pathway for a reflex action
F d. is a partial pathway for a reflex action
F e. has no receptor

Q. 157. **Conditioned reflexes**
T a. are acquired
T b. can be established.
T c. can be abolished

F d. are inherent
F e. can not be abolished

Q. 158. **Uncondition reflexes**
T a. can not be altered
T b. are also called inborn reflex.
T c. are inherent
F d. are acquired
F e. can be altered.

Q. 159. **Withdrawal reflex**
T a. response is inhibition of extensor muscle
T b. occurs in response to noxious stimuli
T c. response is flexor muscle contraction
F d. response is flexor muscle relaxation
F e. is a typical monosynaptic reflex.

Q. 160. **Regarding knee jerk**
T a. its receptor is muscle spindle
T b. it is a stretch reflex
T c. it is monosynaptic reflex
F d. it is polysynaptic reflex
F e. its efferent nerve is femoral nerve.

Q. 161. **A reflex action**
T a. may be carried out by all muscles and secretory glands
F b. is not influenced by higher center in the brain
F c. is a voluntary response to a stimulation.
F d. is usually initiated by higher centre
F e. is always inborn in nature.

Q. 162. **The flexor withdrawal reflex is a**
T a. spinal cord reflex
T b. polysynaptic reflex
T c. protective reflex
F d. monosynaptic reflex
F e. muscle stretch reflex

Q. 163. **Maintenance of upright posture and balance depends upon**
T a. inputs from the eyes, vestibular apparatus and somatic proprioceptors
T b. the body's center of gravity which must be maintained over the body base
F c. contraction of the flexor group of skeletal muscle
F d. only on the vestibular apparatus
F e. only on the proprioceptors.

Q. 164. **Postural reflexes are**
T a. optical weighting reflexes
T b. positive supporting reaction
T c. stretch reflexes
F d. superficial reflexes
F e. autonomic reflexes

Muscle tone & Motor unit

Q. 165. **Muscle spindle is**
T a. Receptor for myotatic or stretch receptor reflex
F b. Receptor for a variety of multisynaptic reflexes
F c. Occurs only in antigravity extensor muscles
F d. Excited by both stretch and contraction of the muscles in which it is located
F e. All of the above.

Q. 166. **A twitch of motor unit is called**
T a. Fasciculation
F b. Myoclonic jerk
F c. Tremor
F d. Chorea
F e. Golgi tendo reflex.

Q. 167. **Curare in therapeutic doses**
T a. Decreases the amplitude of skeletal muscle potential
F b. Prevents propagation of action potential in skeletal muscle
F c. Enhances the action of choline esterase
F d. Enhances the action of catecholamines
F e. Incereases propagation of action potential in skeletal muscle

Q. 168. **Muscle tone is increased by**
T a. gamma efferent impulese to muscle spindle
T b. extrapyramidal lesion
T c. upper motor neuron lesion
F d. lower motor neuron lesion
F e. cerebellar lesions

Q. 169. **Motor units**
T a. in large postural muscles have high innervation ratio
T b. consist of a single motor neuron supplying many muscle fibers
F c. consist of a single muscle fiber innervated by many motor neutrons
F d. can increase force of contraction
F e. contain gamma motor neutrons.

Q. 170. **Intrafusal muscle fiber**
T a. has no or few actin and myosin filament in central region
T b. is innervated by γ efferent fiber
T c. does not contract in its central portion
F d. has more actin and myosin filament in central region
F e. is innervated by α efferent fiber.

Q. 171. **Muscle spindle**
T a. has both intrafusal and extrafusal muscle fiber
T b. is the sensory receptor of muscle
T c. has intrafusal muscle fiber

F d. has no intrafusal muscle fiber
F e. has no extrafusal muscle fiber.

Q. 172. **Golgi tendon organs**
T a. are the receptors of muscle tendon
T b. transmit information about tendon tension
F c. are the receptors of muscle
F d. transmit information about change of muscle fiber length
F e. transmit no information about tendon tension

Q. 173. **Regarding muscle stretch reflex**
T a. reciprocal inhibition relaxes muscles
T b. it is antagonistic to the stretched muscle
T c. the muscle spindles ate sensitive to changes in muscle length
F d. the sensitivity of the muscle spindle can be reduced by increasing the activity of gamma motor neutrons
F e. the reflex arc is polysynaptic.

Q. 174. **Muscle tone is diminished or lost when**
T a. all peripheral nerves innervating a particular muscle are cut
T b. α-motor neutrons are destroyed.
T c. spinal cord ventral root efferent are cut
F d. corticospinal tracts are damaged
F e. basal ganglial structures are damaged

Q. 175. **In a highly trained distance runner, muscle tissue increases in**
T a. enzymes for oxidative phosphorylation
T b. myoglobin content
T c. mass due to hypertrophy of individual fibers
F d. mass due to increase in number of muscle fibers
F e. mass due to an increase in blood supply.

Q. 176. **Rapid eye movement**
T a. is usually associated with active bodily muscle movement
T b. is characterized by irregular heart rate
T c. is characterized by irregular respiratory rate
F d. is usually not associated with muscle movement
F e. causes decreased brain metabolism.

Tract

Q. 177. **Injection of hypertonic saline into which area causes diuresis**
T a. Supraoptic nucleus
F b. Paraventricular nucleus
F c. Preoptic nucleus
F d. Posterior pituitary
F d. Anterior pituitary.

Q. 178. **In the neurohypophysis, secretory granules accumulate in**
T a. Nerve endings
F b. Pituicytes
F c. Intercellular spaces
F d. Capillary endothelium
F e. Axon.

Q. 179. **Decreased hypothalamic function casues depressed levels of the following homones**
T a. Growth hormone
T b. TSH
T c. ACTH
F d. Prolactin
F e. Oxytocin.

Q. 180. **One of the following is a function of hypothalamus**
T a. Homeostasis of temperature
F b. Swallowing
F c. Vomiting
F d. Respiration
F e. Diglutation.

Q. 181. **Profound hypothermic signs include**
T a. Slow breathing
T b. Bradycardia
T c. Hypotension
F d. Hyperactivity
F e. Hypoactivity

Q. 182. **Which of the following are true of median eminence**
T a. Portion of ventral hypothalamus
T b. Hypothalmo-hypophyseai vessels arise here
T c. Outside the blood-brain barrier
F a. Portion of dorsal hypothalamus
F d. All are correct

Q. 183. **What is the mechanism by which infection causes fever**
T a. Pyrogens acting independent of hypothalamus
T a. Effects of inflammatory mediator.
F b. Increased heat production and decreased heat loss
F c. Decreased heat production and decreased heat loss
F d. None of the above

Q. 184. **Ascending tracts are**
T a. spino-olivary tract
T b. fasciculus gracilis
T c. fascicutus cuneatus
F d. rubrospinal tract
F e. vestibulospinal tract.

Q. 185. **Descending tracts are**
T a. extra pyramidal tract
T b. pyramidal tract
T c. corticobulbar tract

F d. spinocortical tract
F e. spin-olivary tract.

Q. 186. **Extrapyramidal tracts are**
T a. reticulospinal tract
T b. tectospinal tract
T c. rubrospinal tract
F d. fasciculus tract
F e. lateral spinothalamic tract.

Q. 187. **Functions of tract of gall are to carry**
T a. kinesthetic sensation from lower part of the body
T b. senses of vibration.
T c. fine touch from lower half of the body
F d. fine touch from upper half of the body
F e. pain sensation

Q. 188. **Sensations transmitted through dorsal column medial leminical system are**
T a. pressure sensation.s
T b. touch sensation
T c. position senses from joints
F d. thermal sensation
F e. pain sensation.

Q. 189. **Spinothalamic tracts transmit**
T a. pain sensation
T b. thermal sensation
T c. sexual sensation.
F d. vibration
F e. proprioception

Q. 190. **Antero-lateral column carries the following sensation**
T a. cold
T b. itching.
T c. crude touch
F d. pressure
F e. position senses.

Q. 191. **Tract of gall**
T a. has a higher degree of spatial orientation of the nerve fibers in respect to their origin
T b. carries position senses from the lower part of the body
T c. carries rapidly transmitted sensations
F d. carries pain sensation
F e. is formed by C-fibers.

Q. 192. **Lateral spinothalamic tract**
T a. transmit thermal sensation
T b. is a cruder type of transmission system
F c. formed by A α fibers
F d. carries proprioception
F e. transmit sensory information that must be transmitted rapidly

Q. 193. **Regarding dorsal spino-thalamic tract**
T a. the second order neuron start from tract of lissauer
T b. it terminates in the thalamus
T c. it occupies the lateral column of spinal cord
F d. the second order neuron start from posterior horn cell.
F e. it terminates in precentral gyrus.

Q. 194. **Functions of extrapyramidal tracts are to maintain**
T a. movement of eye ball
T b. posture
T c. muscle tone
T d. equilibrium
F e. kinesthetic sensation.

Q. 195. **Regarding corticospinal tract**
T a. the fibers originate from giant pyramidal cells
T b. it transmits motor signals directly from cortex to spinal cord
T c. it contains more than 1 million fibers.
F d. the fibers are mostly unmyelinated.
F e. the fibers mostly cross in lower part of pons.

Q. 196. **Pain stimulants are**
T a. bradykinin
T b. prostaglandin
T v. histamine
F d. epinephrine
F e. oxytocin.

Q. 197. **Pain is**
T a. unpleasant sensation due to tissue damage
T b. mainly a protective mechanism for body
T c. produced by histamine
F d. produced by epinephrine
F e. produced by sodium.

Q. 198. **Alternative name of fast pain includes**
T a. pricking pain
T b. acute pain
T c. sharp pain
F d. aching pain
F e. throbbing pain.

Q. 199. **Alternative name of slow pain are**
T a. nauseous pain
T b. throbbing pain
T c. chronic pain
F d. electric pain
F e. pricking pain.

Q. 200. **Tracts through which pain sensation transmitted are**
T a. paleospinothalamic
T b. neospinothalamic
F c. rubrospinal

F d. vestibulospinal
F e. corticospinal.

Q. 201. **Fast pain is**
T a. elicited by thermal stimuli
T b. felt within 0.1 second
T c. elicited by mechanical stimuli
F d. elicited by chemical pain stimuli
F e. felt within 0.6 second.

Q. 202. **Fast pain is**
T a. transmitted through neospinothalamic tract
T b. stimulated by glutamate
T c. Transmitted through Aδ fiber
F d. transmitted through C fiber
F e. transmitted through paleospinothalamic tract.

Q. 203. **Brown-Sequard's syndrome is characterized by the loss of**
T a. voluntary movements on the same side
T b. pain sensation on the opposite side
F c. thermal sensation on the same side
F d. position sensation on the opposite side
F e. two-point discrimination on the opposite side.

Q. 204. **Extrapyramidal motor system lesion causes**
T a. lead pipeparalysis
T b. an abnormal gait with small fast regular step
T c. tremor at rest
F d. muscle paralysis
F e. muscle wasting.

Q. 205. **Anterolateral system carries following**
T a. pressure
T b. pain
T c. temperature
F d. vibration
F e. position sensation.

Q. 206. **Pyramidal tract**
T a. conveys impulse for movement of finger and hand
T b. is related to superficial reflexes
F c. controls movement of eye ball
F d. maintains equilibrium
F e. carries pain sensation.

Cerebral cortex

Q. 207. **Skilled voluntary movement is initiated at**
T a. Cerebral cortex (motor cortex)
F b. Basal ganglia
F c. Cortical association areas
F d. Cerebellum
F d. Medulla.

Q. 208. **All of the following manifestations are seen in cases of cerebellar damage in human beings except**
T a. Ataxia, atonia and asthenia.
T b. Loss of non-declarative/reflexive memory
T c. Loss of adjustment of vestibulo-ocular reflex
F d. Static tremour and rigidity.

Q. 209. **Destruction of sensory area 1 of brain leads to loss of which sensations?**
T a. Sterognosis & 2 point discrimination
F b. Pain
F c. Touch
F d. Sterognosis gone but 2 point discrimination retained
F e. Temperature.

Q. 210. **The following relay in sensory cortex**
T a. Pain
T b. Touch
T c. Temperature
F d. Olfaction
F e. Vision.

Q. 211. **Pyramidal fibers are**
T a. Projection fibres
F b. Association fibres
F c. Commissural fibres
F d. Association fibres and commissural fibres
F e. All of the above.

Q. 212. **Broca's area : which is true**
T a. Supplied by MCA (middle cerebral artery)
F b. Present bilaterally in brain
F c. Lesion causes Laryngeal palsy
F d. Present in the temporal lobe
T e. Supplied by ACA (anterior cerebral artery).

Q. 213. **For each 1° F rise of temperature, cerebral blood flow falls by**
T a. 4%
F b. 1%
F c. 2%
F d. 7%
F d. 6%.

Q. 214. **Temopral lobe lesion causes**
T a. Homonymus upper quadrantinopia
F b. Homonymus lower quadrantinopia
F c. Bi-temporal hemianopia
F d. Bi-nasal hemianopia
F e. Protanopia.

Q. 215. **Damage to sensory area 1 of the cerebral cortex results in**
T a. Loss of tactile and two point discrimintion
F b. Loss of perception of pain

F c. Loss of perception of touch
F d. Loss of only tactile discrimintion
F d. Loss of only discrimintion.

Q. 216. **Vomiting centre is situated in the**
T a. Amygdala
F b. Hypothalamus
F c. Pons
F d. Medulla
F e. Thalamus.

Q. 217. **Broca's area is present in**
T a. Inferior frontal gyrus
F b. Superior temporal Gyru
F c. Precentral gyrus
F d. Post central gyrus
T a. Inferior temporal gyrus.

Q. 218. **Motor area of Bradman is area**
T a. 4
F b. 1
F c. 5
F d. 7
F e. 17

Q. 219. **Layers of cerebral cortex are**
T a. external pyramidal layer
T b. internal granular layer
T c. molecular layer
T d. external granular layer
F e. layers of rods and cones.

Q. 220. **Storage of information**
T a. is located in cerebral cortex
T b. causes future thinking process with its large fraction
T c. causes response with its small fraction
F d. causes response with its large fraction
F e. causes future thinking process with its small fraction.

Q. 221. **Study of living brain have been dramatically enhanced by the development of the following new imaging techniques**
T a. computerized tomography
T b. positron emission tomography
T c. magnetic resonance imaging
T d. angiography
F e. electroencephalography.

Cerebellum

Q. 222. In parkinsonism, tremor is :
T a. 6-8 per second
F b. 2 per second
F c. 2-4 per second
F d. uncountable
F e. 1 per second

Q.223. **Vestibular fibres relay in**
T a. Floculonodular lobe of cerebellum
F b. Vermis
F c. Lateral geniculate body
F d. Auditory cortex
F e. Medial geniculate body.

Q. 224. **Floculonodular lobe of cerebellum is concerned with**
T a. Equilibrium
F b. Co-ordination
F c. Baroreception
F d. Chemoreception
F e. Olfaction.

Q. 225. **The cerebellum**
T a. Has a totally inhibitory output from its cortex
F b. Has only excitatory signal output from its deep nuclear layers
F c. Has a conscious interpretation of motor activity
F d. Has inhibitory influence on muscle tone in humans
F e. All of the above.

Q. 226. **Purkinjee cell is a**
T a. Output cell
F b. Input cell
F c. Inter neuron
F d. Connector neuron
F e Ganlion cell.

Q. 227. **In cerebellar disease, the correct statements are**
T a. The Rombergs sign is positive
T b. There is Adiodokokinesis
T c. There is pendular knee jerk
F d. There is involuntary tremor response.

Q. 228. **Cerebellum is important in controlling of**
T a. movement maintenance
T b. balance maintenance
T c. accuracy of muscle movement
T d. smooth muscle movement
F e. initiating voluntary muscle movement

Q. 229. **Disease of one cerebellar hemisphere would likely results in**
T a. past pointing
T b. a tendency to fall toward the side of the lesion.
F c. involuntary tremor
F d. spastic paralysis
F e. bradykinesia

Q. 230. **Efferent fibers connecting the cerebellum are**
T a. fastigio-vestibular tract
T b. fastigio-bulbar tract

T c. cerebello-olivary tract
F d. dorsal spino-cerebellar tract
F e. vestibulo-cerebellar tract

Q. 231. **Disorders of the cerebellum cause**
T a. symptoms ipsilateral to the defect
T b. weakness of movements so that movements are carried out slowly
T c. ataxia
F d. increased muscle tone
F e. exaggerated deep reflexes.

Q. 232. **Cerebellum**
T a. responds to vestibular stimuli and assists in maintaining equilibrium
T b. plays important role in progression from one movement to the next
T c. facilitates a smooth, co-ordinated voluntary movements
F d. does not play an active role in maintenance of posture
F e. receives sensory information.

Q. 233. **Effect of cerebellar lesion are**
T a. asthenia
T b. ataxia
T c. hypotonia
F d. paralysis
F e. perkinsonism.

Q. 234. **Afferent fibers connecting the cerebellum are**
T a. vestibulo-cerebellar tract
T b. olivo-cerebellar tract
T c. dorsal spino-cerebellar tract
F d. fastigio-vestibular tract
F e. cerebello-olivary tract.

Q. 235. **Functions of the cerebellum are**
T a. prediction of future position of moving parts of the body
T b. prediction of rates of progression of visual phenomenon
T c. error control of movement
F d. initiation of motor activity
F e. appreciation of sensation.

Q. 236. **Equilibrium is controlled by**
T a. cerebellum
T b. reticular substance
T c. mesencephalon
F d. limbic system
F e. basal ganglia.

Hypothalamus

Q. 237. **Injection of hypertonic saline into which area causes diuresis**
T a. Supraoptic nucleus
F b. Paraventricular nucleus
F c. Preoptic nucleus
F d. Posterior pituitary
F d. Anterior pituitary.

Q. 238. **In the neurohypophysis, secretory granules accumulate in**
T a. Nerve endings
F b. Pituicytes
F c. Intercellular spaces
F d. Capillary endothelium
F e. Axon.

Q. 239. **Decreased hypothalamic function casues depressed levels of the following homones**
T a. Growth hormone
T b. TSH
T c. ACTH
F d. Prolactin
F e. Oxytocin.

Q. 240. **One of the following is a function of hypothalamus**
T a. Homeostasis of temperature
F b. Swallowing
F c. Vomiting
F d. Respiration
F e. Diglutation.

Q. 241. **Profound hypothermic signs include**
T a. Slow breathing
T b. Bradycardia
T c. Hypotension
F d. Hyperactivity
F e. Hypoactivity

Q. 242. **Which of the following are true of median eminence**
T a. Portion of ventral hypothalamus
T b. Hypothalmo-hypophyseai vessels arise here
T c. Outside the blood-brain barrier
F a. Portion of dorsal hypothalamus
F d. All are correct

Q. 243. **What is the mechanism by which infection causes fever**
T a. Pyrogens acting independent of hypothalamus
T a. Effects of inflammatory mediator.
F b. Increased heat production and decreased heat loss
F c. Decreased heat production and decreased heat loss
F d. None of the above

Q. 244. **Hypothalamus**
T a. inhibits sympathetic nerve in hot weather
T b. causes vasodilatation in hot weather
T c. inhibits parasympathetic nerve in cold environment

F d. stimulates parasympathetic nerve in cold environment
F e. stimulates sympathetic nerve in hot weather.

Q. 245. **Hypothalamus**
T a. regulates the activity of anterior pituitary gland
T b. regulates body temperature
T c. participates in the integrated control of CVS
F d. maintains rhythmic breathing
F e. controls the voluntary movements of the body.

Q. 246. **Hypothalamus**
T a. is the centre for emotion and personality
T b. regulate body temperature
T c. is the centre for autonomic nervous system.
F d. is the centr for somatic nervous system
F e. has no endocrine function.

Q. 247. **Thalamus**
T a. is situated in the midbrain and part of fore brain
T b. is an important reflex center
T c. is a collection of gray matter containing nerve cells
F d. is situated in the hind brain
F e. regulates body temperature.

Q. 248. **Functions of different nuclei of hypothalamuse include**
T a. ventro-medial nucleus causes satiety
T b. lateral nucleus causes thirst and eating
F c. posterior nucleus causes increased heat loss
F d. anterior nucleus causes decreased heat loss
F e. supra-optic nucleus causes secretion of oxytocin.

Q. 249. **Posterior nucleus of hypothalamus**
T a. causes vasoconstriction
T b. inhibits parasympathetic nerve
T c. stimulates sympathetic nerve
F d. inhibits sympathetic nerve
F e. stimulates parasympathetic nerve.

Q. 250. **Posterior nucleus of hypothalamus**
T a. decreases heat loss
T b. is activated in cold weather
F c. causes vasodilatation
F d. is activated in hot weather
F e. increases heat loss.

Q. 251. **Anterior nucleus of hypothalamus**
T a. inhibits sympathetic nerve
T b. causes vasodilatation
T c. stimulates parasympathetic nerve
F d. stimulates sympathetic nerve
F e. inhibits parasympathetic nerve.

Q. 252. **Anterior nucleus of thalamus**
T a. increases heat loss
T b. is activated in hot environment
F c. causes vasoconstriction
F d. is activated in cold environment
F e. decreases heat loss.

Basal ganglia/limbic system

Q. 253. **Stereoanesthesia is due to lesion of**
T a. Nucleus cuneatus
F b. Nucleus Gracilis
F c. Spinoreticular tract
F d. Spinothalamic tract
F e. All of the above.

Q. 254. **Where is motor activity probably initiated in the brain?**
T a. Basal ganglia
F b. Motor cortex
F c. Premotor cortex
F d. Cerebellum
F e. Pons.

Q. 255. **Vomiting centre is situated in the**
T a. Amygdala
F b. Hypothalamus
F c. Pons
F d. Medulla
F e. Mid brain.

Q. 256. **Hyperkinetic syndromes such as chorea and athetosis are usually associated with pathological changes in**
T a. Basal ganglia complex
F b. Motor areas of cerebral cortex
F c. Anterior hypothalamus
F d. Pathways for recurrent collateral inhibition in the spinal cord
F e. Pons

Q. 257. **Arousal response is mediated by**
T a. Reticulo activating system
F b. Dorsal column
F c. Spinothalamic tract
F d. Vestibule cerebellar tract
F e. Spinothalamic tract.

Q. 258. **During light sleep, the sleep spindles that appear have the frequency of**
T c. 14-16 /second
F a. 1-2 /second
F b. 6-12 /second

F d. 21-26 /second
F c. 6-8 /second.

Q. 259. **Headache can be produced by**
T a. Dilatation of intracranial blood vessels
T b. Presence of blood in CSF
T c. Loss of CSF following lumbar puncture
F d. Mechanical damage to parietal cortex
F e. Mechanical damage to temporal cortex.

Q. 260. **The condition known as REM sleep is**
T a. Referred to as paradoxcal sleep
F b. That point at which the indivudual becomes aware and alert
F c. Characterized by total lack of all muscular activity
F d. Charactrized by slow high voltage regular EEG activity
F e. All of the above.

Q. 261. **In a person with a history of alcohol abuse which of the following aspects of memory is most likely to be impaired?**
T a. Recall of events occuring a few weeks previously
F b. Accurate perception of stimuli
F c. Immediate recall of new information
F d. Recall of events in the remote past
F e. Recognition of familiar objects

Q. 262. **The basal ganglia controls**
T a. simple gross movement
T b. complex pattern of movement
T c. body equilibrium
F d. relative intensity of movement
F e. reflex movement.

Q. 263. **Basal ganglia dysfunction is characterized by**
T a. lead-pipe rigidity
T b. bradykinesia
F c. hypotonia
F d. intention tremor
F e. dysmetria.

Q. 264. **Basal ganglia**
T a. lesion produces tremor in the distal joints
T b. helps to prepare the body for movements.
T c. enables the trunk and limbs to be placed in appropri -ate positions before the motor cortex activates discrete movements
F d. lesion usually reduces muscle tone
F e. lesion produces incordination of movements.

Q. 265. **Important structures comprising the limbic system are**
T a. amygdala
T b. hippocampus
T c. hypothalamus
F d. cerebellum
F e. cerebral cortex.

Q. 266. **Slow wave sleep**
T a. is characterized by vegetative functions of the body
T b. is broken periodically by rapid eye movement sleep
T c. occurs during the first hour of sleep
F d. is exceedingly unrestful
F e. is associated with 10 to 30% increase of blood pressure.

Q. 267. **During deep sleep there is a fall in**
T a. metabolic rate
T b. urine formation
F c. hand skin temperature
F d. arterial PCO_2
F e. growth hormone and cortisol ratio.

Q. 268. **Effects of lesion in basal ganglia are**
T a. hemibalismus
T b. Perkinsonism
T c. chorea
F d. insomnia
F e. nystigmus.

Q. 269. **Basal ganglia consists of**
T a. putamen
T b. subthalamic nucleus.
T c. caudate nucleus
F d. hypothalamus
F e. thalamus.

Q. 270. **Limbic system consist of**
T a. amygdala
T b. hypothalamus
T c. orbitofrontal gyrus
F d. thalamus
F e. cerebellum.

EEG

Q. 271. **The frequency of alpha waves in EEG is**
T a. 8 to 12 cycles/second
F b. 15-25 cycles/second
F c. 2-5 cycles/second
F d. None of the above

Q. 272. **The electroencephalographic (EEG) curves are called**
T a. Berger's rhythm
F b. ABCDE curves
F c. Neurogenic rhythm
F d. REM rhythm

Q. 273. **EEG rhythm recorded from the surface of the scalp during REM sleep:**

T a. Beta
F b. Alpha
F c. Delta
F d. Theta

Q. 274. **The frequency of Beta waves (per sec) in EEG is** :

T a. 13-30
F b. 0-4
F c. 4-7
F d. 7-13
F e. 2-5.

Q. 275. **Which of the following is wrongly matched about EGG waves and their duration :**

T a. Q wave- 0.10 second
F b. P wave - 0.10 second
F c. S wave - 0.04 second
F d. QRS complex- 0.10 second.

Q. 276. **Buerger waves (alpha waves) of EEG have the rhythm per second of**

T a. 8-13
F b. 0-4
F c. 4-7
F d. 13-30

Q. 277. **An EEG**

T a. Is bilaterally symmetrical
F b. Provides indication of intelligence
F d. Tends to show waves of smaller amplitude during deep sleep than of alert state
F e. Show waves with a lower frquency during intense thought than during sleep.

Special Senses

Different special senses with their organ

Special senses	*Organ*	*Receptor*
1. Vision	1. Eye	1. Rods and cones
2. Hearing	2. Ear (organ of corti)	2. Hair cells
3. Taste	3. Tongue	3. Taste bud
4. Smell	4. Olfactory mucous membrane	4. Olfactory neurones
5. Rotational acceleration	5. Ear (semicircular canals)	5. Hair cells
6. Linear acceleration.	6. Ear (utricle and saccule).	6. Hair cells.

(Ref. Ganong 22th Edition, page-122)

Q. 00. **What are the effects of vit-A deficiency in eye?**

Ans. Deficiency sings (consequences of vitamin A deficiency) :

1. ***Eye changes*** : Deficiency causes disintrigation of epithelium of cornea and lacrimal gland causes--
   a. Night blindness (nyctalopia) : This is the earliest change and is due to les formation of rhodopsin.
   b. Xeropthalmia : Cojunctival kertinization.
   c.Keratomalacia : Corneal softening and ulceration.
   d. Bitot's sports : Triangular, shiny, gray (white plaques) spots on the conjunctiva.
   e. Corneal scarring and blindness.

Q. 01. **How vitamin A deficiency can be prevented?**

Ans. Vitamin A deficiency can be prevented by :

1. Improvement of diet.
2. *Vitamin A* fortified food (sugar fortified with vit-A)
3. Prophylactic use of high potency oral vitamin-A capsule in the high risk children.
4. Health education of the people.

(Ref. Community medicine; J, E. Park)

Eye

Eye is the principal organ of vision. It is located in the eye ball with accessory visual apparatus.

Functional anatomy

Covering of eye ball : Eyeball has three coats or tunics from outwards to inwards :

a. ***Outer fibrous coat*** : It consists of two parts :
   i. Sclera : posterior 5/6 th, which is opaque.
   ii. Cornea : anterior 1/6 th, which is transparent.

   Limbus : The junction between the sclera and cornea.

   Functions of the outer coat :
   1. Sclera is responsible for maintaining the shape & form of eye ball.
   2. Sclera and cornea converts the eye ball into a closed chamber.
   3. Cornea is the main refracting surface of the eye.

b. *Middle vascular coat* : This coat lies just underneath the sclera. It consists of three parts from behind forward :
   i. *Choroid* : Choroid is a dark brown, highly vascular layer situated between the slera and retina.
   ii. *Cilliary body* : Cilliary body is triangular in shape with base forwards. The iris is attached to the middle of the base. It consists of non-striated muscle fibres (*cilliary muscles*), stroma and secretory epithelial cells. It consists of two main parts namely pars plicata and pars plana
   iii. *Iris* : Iris is a coloured, free, circular diaphram with an aperture in the centre- the *pupil*. It consists of endothelium,stroma, pigment cells and two group of plain muscle fibres, one circular (*spincter pupillae*) and the other radiating (*dilator pupillae*).

   Functions of the middle coat :
   a. It is concerned with nutrition of the eye ball.
   b. Aquous humour is formed by the epithelium covering of the cilliary body.
   c. Action of cilliary muscles regulate the anterior curvature of the lens and thus helps in focussing the object on the retina.
   d. The iris muscle regulate the size of pupil.

c. ***Inner nervous coat*** : This is the receptive and conducting part of the eye ball and forms its innermost layer consisting of several layers of cells of retina.

   Functions of the inner coat : It is concerned with vision and various other reflexes which are evoked by light stimulus.

Refractive media

Refractive media	*Refractive power*
i. Cornea	1.38
ii. Aqueous humor	1.33
iii. Lens	1.40
iv. Vetrious body	1.34

(Ref. Guyton & Hall 11th edition)

Cornea

Cornea is the anterior modified part of the sclera It is the round, transparent and convexity in the anterior part of the eye ball.

Function :

a. Allows free entry of light
b. Acts as refractive media.

Histology or structure : From outside inward there are the folowing 5 layers :

1. Corneal epithelium or external stratified epithelium: Several layers of cells contineues with conjuctiva :
   i. The superficial four or five layers are stratified squamous.
   ii. The deepest (basal) layer is columnar.
   iii. The intermediate two or three layers are polyhedral
2. Bowman's capsule or anterior elastic lamina.
3. Susbtantia propria or coneal stroma.
4. Descemet's membrane or posterior elastic lamina.
5. Corneal endothelium or inner layer of squamous epithelium.

Nutrition of cornea : Cornea is avascular. It's epithelium, corneal corpuscles and endothelium get nutrition and O_2 supply from :

a. Aqueous humour
b. The superficial marginal plexus of capillaries at the limbus.
c. The capillaries in the tarsal conjunctiva.
d. O_2 dissolved in the layer of tear film on the epithelial surface.

Aqeous Humour

Aqueous humour is a clear watery fluid occupying both the anterior and posterior chambers of the eye.

Composition :

1. Water : 98.69 %
2. Solids : 1.31 %
   a. Colloids : Much less than serum.
   b. Chlorides : Much higher than serum.

Formation : Formed by the *enzymatic activity* of the cilliary process and is secreted mainly by active transport.

Circulation of aqeous : Cilliary process → Posterior chamber of eye → Through pupil → Aterior chamber of eye → Iridiocorneal angle → Canal of Schlemm → Episcleral vein → Aqueous vein → Opthalmic vein.

Functions :

a. Maintains intra occular pressure and shape of the eye ball.
b. Acts as refractive media.
c. Supplies nutrition to and drains the metabolis from the surrounding structures.

Pupil

Pupil is the central round aperture within the iris. The normal size of the pupil is 3-4 mm.

i. *Miosis* : Contraction of the pupil is called miosis.
ii. *Mydriasis* : The dilation of the pupil is called mydriasis.

Functions :

1. Pupil modifies the amount of the light entering the eye.
2. Pupil controls the depth of focus of the optical system of eye. Smaller pupil increases the depth of the focus.
3. Acuity of vision is dependent upon pupillary size.

Iris

Iris is a circular disc of the anterior part of the coroid situated in between cornea and lens. It has a central rounded aperture called pupil.

Histology : Histologically iris consist of following layers.

1. Squamous endothelium.
2. Anterior border layer.
3. Vessel layer or stroma
4. Muscles-spincter pupillae and dilator pupillae
5. Pigment epithelium.

Nerve supply :

a. *Sphinter pupillae :* supplied by *parasympathic* which arises from the Edenger westphal nucleus of 3rd cranial nerve via occulomotor nerve, cilliary ganglion and short cilliary nerve.
b. *Dilator pupillae :* supplied by *sympathetic arising* from superior cervical ganglion.

Function :

1. Act as a adjustable diaphragm by maintaining the diameter of pupill and the quantity of entry of light.
2. Increase the depth of focus.

Lens of eye

It is the chief refracting media of the eye ball having the maximum refractive power. It is transparent, elastic and bi-convex, enclosed in a cpasule. Posteriorly, it is more convex. It is circular about 11 mm in diameter. The thickness in the centre is about 3.6-3.9 mm. Refractive index - 1.4 at the centre, less in the periphery. It is held in situ by suspensory ligament.

Structure : The lens consists of three elements :

a. *Capsule :* Forms a trasparent structureless membrane.
b. *Anterior epithelium :* It is formed by a single row of cuboidal or low columnar cell which cover the anterior surface only.

c. *Lens substance :* Composed of concentric layers of elongated modified cells. The peripheral parts are soft & nucleated; central part forms a dense non-nucleated mass.

Nutrition : It has no vascular supply. It gets its nutrition almost entirely from the aqueos humour and partly from the vitreous humour.

Function : It refract light from distant or near objects into a focus exactly on the retina and thus aids in vision. It absorbs all rays below 300 nm or above 2500 nm.

Vitreous Humour (Body)

It is a jelly like transparent substance, is enclosed by a thin homogeneous membrane; the hyaloid membrane, and occupying the posterior compartment of eye.

Structure : It is made up of a series of lamellae arranged concentrically round the hyaloid canal.

The Lamellae composed of flat cells. The space between the lamellae are filed up with fluid.

Refractive index : 1.34

Functions :

1. Acts as a refractive media.
2. It maintains the shape and intraocular pressure of eye ball.
3. It provides nutrition to the lens.
4. It prevents detachment of retina.
5. It supports the lens posteriorty.

Retina

***Layers of retina** : From outside to inside*

i. Pigmented layer
ii. Layer of rods and cones
iii. External limiting membrance
iv. Outer nuclear layer (cell bodies of rods and cones)
v. Outer plexiform (molecular) layer
vi. Inner nuclear (bipolar cells) layer
vii. Inner plexiform (molecular) layer
viii. Ganglionic cell layer
ix. Nerve fibers layer
x. Inner limiting layer.

(Ref. Ganong 22th Edition)

Q. 00. **Briefly describe the vascular supply of the retina.**

Ans. *Arteries, arterioles, and veins of retina* : The arteries, arterioles, and veins in the superficial layers of the retina near its vitreous surface can be seen through the ophthalmoscope. Since this is the only place in the body where arterioles are readily visible. Ophthalmoscopic examination is of great value in the diagnosis and evaluation of *diabetes mellitus, hypertension*, and other diseases that affect blood vessels.

i. The retinal vessels supply the bipolar and ganghion cells
ii. The receptors are nourished for the most part by the capillary plexus in the cboroid. This is why retinal detachment is so damaging to the receptor cells.

(Ref. Ganong 22th Edition)

Description of retina

a. ***Retinal neurons*** : The retina contains four types of neuron :
   i. Bipolar cells
   ii. Ganglion cells
   iii. Horizontal cells
   iv. Aamacrine cells.

b. ***Synapses in retina*** : The rods and cones synapse with bipolar cells, and the bipolar cells synapse with ganglion cells. The axons of the ganglion cells converge and leave the eye as the optic nerve.

c. ***Supporting cells*** :
   i. *Horizontal cells* connect receptor cells to the other receptor cells in the outer plexiform layer.
   ii. *Amacrine cells* connect ganglion cells to one another in the inner plexiform layer. They have no axons, and their processes make both pre and postsynaptic connections with neighboring neural elements.

d. ***Convergence of cells in retina*** : There is considerable overall convergence of receptors on bipolar cells and of bipolar cells on ganglion cells. Gap junctions also connect

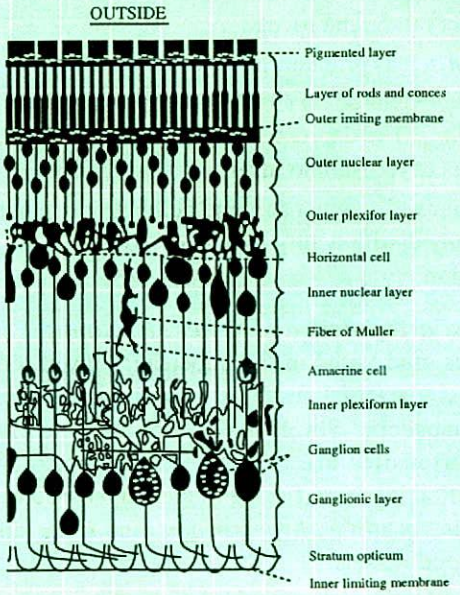


Fig. 17-11. *Layers of Retina*

retinal neuron to one another, and the permeability of these gap junctions is regulated.

e. ***Pigment epithelium*** : Since the receptor layer of the retina

rests on the *pigment epithelium* next to the choroid, light rays must pass through the ganglion cell and bipolar cell layers to reach the rods and cones. The pigment epithehum absorbs light rays, preventing the reflection of rays back through the retina. Such reflection would produce blurring of the visual images.

f. ***External and internal limiting membrane*** : The neural elements of the retina are bound together by glial cells called Muller cells. The processes of these cells form an internal limiting membrane on the inner surface of the retina and an external limiting membrane in the receptor layer.

g. ***Optic disk and blind spot*** : The optic nerve leaves the eye and the retinal blood vessels enter it at a point 3 mm medial to and slightly above the posterior pole of the globe. This region is visible through the ophthalmoscope as the optic disk. There are no visual receptors overlying the disk, and consequently this spot is blind (*the blind spot*).

h. ***Macula lutea and fovea centralis*** : Near the posterior pole of the eye, there is a yellowish pigmented spot, the *macula lutea.*

Fovea centralis : A thinned-out, rod-free portion of the macula lutea. In it, the cones are densely packed, and each synapses to a single bipolar cell which in turn synapses on a single ganglion cell, providing a direct pathway to the brain. There are very few overlying cells and no blood vessels.

Consequently, the *fovea* is the point where visual acuity is greatest. When attention is attracted to or fixed on an object, the eyes are normally moved so that light rays coming from the object fall on the fovea.

Situation : It is situated at a point on retina about 2.5 mm lateral to the margin of the optic papilla.

Formation : The depression is due to lateral displacement of the layers of retina upto layer 5.

Pecularities : It contains no rod cell but only cone cell. So, it is concerned with acuity of vision, colour vision and bright light vision.

i. ***Arteries, arterioles, and veins of retina*** : The arteries, arterioles, and veins in the superficial layers of the retina near its vitreous surface can be seen through the ophthalmoscope. Since this is the one place in the body where arterioles are readily visible, ophthalmoscopic examination is of great value in the diagnosis and evaluation of *diabetes mellitus*, *hypertension*, and other diseases that affect blood vessels.

i. The retinal vessels supply the bipolar and ganghion cells
ii. The receptors are nourished for the most part by the capillary plexus in the cboroid. This is why retinal detachment is so damaging to the receptor cells.

(Ref. Ganong 22th Edition; page 148, 149)

j. **Retinal receptors** *:* Retinal receptors are -

a. ***Rod cell*** : The rod cells are long sylender, highly specialized photorecptor cells found in the retina. It is about 120 million. *(Ref. Ganong 22th Edition)*

Parts of rod cell : It is divided into two parts.

1. Outer segment : It consists of two parts-
   I. Outer part : Thin cylindrical composed of a myelin - like substance and contains rhodopsin.
   II. Inner part : Broad, longitudinaly striated and is protoplasmic.
2. Inner segment : Thinner, consists of a nucleus and a long fibre terminating in end bulb or a spherule.

Functions of rod cell :

i. It concerned with dim light vision and have no play in colour vision & visual acuity.
ii. The outer segment is most sensative which abosrbs light and the inner segment is concerned with metabolic activity of the rod cells.

b. ***Cone Cell*** *:* These are conical photosensative visual cells found in retina. About 6 millions (Ref. Ganong 21th Edition) in each human retina.

Parts of cone cell : It is divided into 2 segments :

1. Inner segment.
2. Outer segment : It consists of two parts -
   a. Outer part contain iodopsin.
   b. Inner part.

Functions of cone cell : Cone cells are concerned with bright light vision, visual acuity and colour vision.

(Ref. Ganong 22th Edition; page 148, 149)

Difference between rod and cone cell

Rods	*Cones*
1. Cylindrical in shape	1. Conical in shape
2. Numerous in pheriphery.	2. Numerous in foeva centrlis.
3. Absent in fobea centralis	3. Numerous in fovea centralis.
4. Visual pigment is rodopsin.	4. Visual pigment is iodopsin.
5 It concerned with dim light vision	5. It concerned with bright, light vision, colour vision, acquity of vision.

Neural pathways & primary visual cortex

Primary visual cortex : The primary visual receiving area (primary visual cortex, Brodmann's area 17; also known as V1), is located principally on the sides of the calcarine fissure.

i. The axons of the *ganglion cells* pass caudally in the *optic nerve* and *optic tract* to end in the lateral geniculate body, a part of the thalamus. The fibers from each nasal hemiretina decussate in the *optic chiasm*. In the *lateral geniculate body*, the fibers from the nasal half of one retina and the temporal half of the other synapse on the cells whose axons form the *geniculocalcarine tract*. This tract passes to the occipital lobe of the cerebral cortex.

ii. Some ganglion cell axons pass from the optic tract to the ***pretectal region*** of the midbrain and the superior colliculus, where they form connections that mediate *pupillary reflexes* and *eye movements*.

iii. The *frontal cortex* is also concerned with eye movement, and especially its refinement. The bilateral ***frontal eye fields*** in this part of the cortex are concerned with control of saccades, and an area just anterior to these fields is concerned with *vergence* and the *near response*.

The frontal areas concerned with vision probably project to the *nucleus reticularis tegmentalis pontinus*, and from there to the other brain stem nuclei mentioned above.

iv. Other axons pass directly from the optic chiasm to the *suprachiasmatic nuclei* in the ***hypothalamus***, where they form connections that synchronize a variety of endocrine and other circadian rhythms with the light-dark cycle.

v. Activation occurs not only in the occiptal lobe but also in parts of the *inferior temporal cortex*, the *posteroinferior parietal cortex*, portions of the *frontal lobe* and the *amygdala*.

vi. The ***subcortical structures*** activated in addition to the lateral geniculate body include the-

a. Superior colliculus
b. Pulvinar
c. Caudate nucleus
d. Putamen
e. Claustrum.

(Ref. Ganong 22th Edition; page 149)

Photoreceptor mechanism

i. ***Ionic basis of photoreceptor potentials in rods and cones*** : Na^+ channels in the outer segments of the *rods* and *cones* are open in the dark, so current flows from the inner to the outer segment. Current also flows to the synaptic ending of the photoreceptor. *Na^+-K^+ ATPase* in the inner segment maintains ionic equilibrium. Release of synaptic transmitter is steady in the dark. When light strikes the outer segment, the reactions that are initiated close some of the Na^+ channels, and the result is a hyperpolarizing receptor potential. The hyperpolarization reduces the release of synaptic transmitter, and this generates a signal that ultimately leads to action potentials in ganglion cells. The action potentials are transmitted to the brain.

(Ref. Ganong 22th Edition; page 157)

ii. ***Photosensitive compounds*** : The photosensitive compounds in the eyes of humans and most other mammals are made up of-

a. *Opsin* : a protein
b. *Retinene*$_1$, the aldehyde of vitamin A_1. Since the retinenes are aldehydes, they are also called retinals. The A vitamins themselves are alcohols and are therefore called retinols.

(Ref. Ganong 22th Edition; page 157)

iii. ***Rhodopsin*** : The photosensitive pigment in the *rods* is called rhodopsin or *visual purple*. Its opsin is called scotopsin. Rhodopsin has a peak sensitivity to light at a wave length of 505 nm.

a. Molecular weight : 4 1,000.

b. It is found in the membranes of the rod disks and makes up 90% of the total protein in these membranes.

It is one of the many serpentine receptors coupled to G proteins. Retinene$_1$ is parallel to the surface of the membrane and is attached to a lysine residue at position 296 in the seventh transmembrane domain.

(Ref. Ganong 22th Edition; page 158)

iv. ***Phototransduction mechanism*** : *In the dark*, the retinene$_1$ in rhodopsin is in the *11-cis configuration*. The only action of light is to change the shape of the retinene, converting it to the *all-trans isomer*. This in turn alters the configuration of the opsin, and the opsin change activates the associated heterotrimeric G protein, which in this case is called ***transducin*** or G_{t1}. The G protein exchanges GDP for GTP, and the α subunit separates. This subunit remains active until its intrinsic *GTPase* activity hydrolyzes the GTP. Termination of the activity of transducin is also accelerated by its binding of β-arrestin.

The α subunit activates cGMP phosphodiesterase, which converts cGMP to 5'-GMP. cGMP normally acts directly on Na^+ channels to maintain them in the open position, so the decline in the cytoplasmic cGMP concentration causes some Na^+ channels to close. This produces the hyperpolarizing potential. The hyperpolarization reduces the release of synaptic transmitter, and this generates a signal that ultimately leads to action potentials in ganglion cells. The action potentials are transmitted to the brain.

(Ref. Ganong 22th Edition; page 158)

Sequence of events involved in phototransduction in rods and cones :

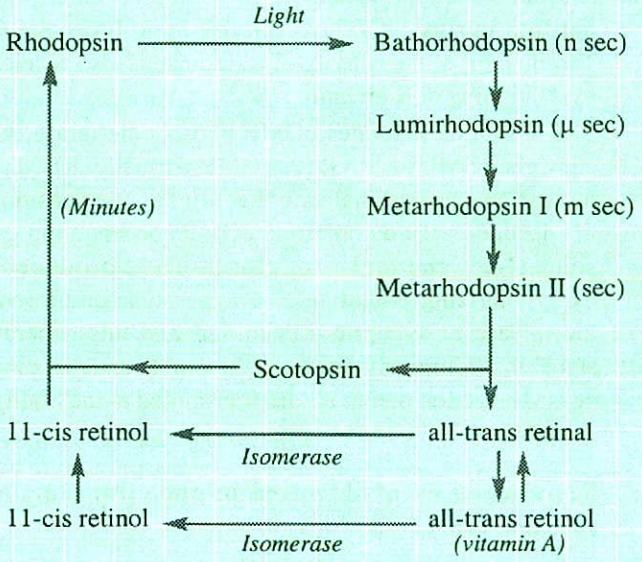
Incident light
↓

Structural change in the retinene$_1$ of photopigment
↓
Conformational change of photopigmen
↓
Activation of transducin
↓
Activation of phosphodi- esterase
↓
Decreased intracellular cGMP
↓
Closure of Na^+ channels
↓
Hyperpolarization
↓
Decreased release of synaptic transmitter
↓
Response in bipolar cells and other neural elements.

(Ref. Ganong 21th Edition; page 159)

v. ***Cyclic resynthesis of rhodopsin*** : After retinene$_1$ is converted to the *all-trans configuration*, it separates from the opsin (bleaching). Some of the rhodopsin is regenerated directly, while some of the retinene$_1$ is reduced by the enzyme alcohol dehydrogenase in the presence of NADH to *vitamin A$_1$*, and this in turn reacts with scotopsin to form ***rhodopsin***. All of these reactions except the formation of the all-trans isomer of *retinene$_1$* are independent of the light intensity, proceeding equally well in light or darkness. The amount of rhodopsin in the receptors therefore varies inversely with the incident light level.

(Ref. Ganong 22th Edition; page158)



(Ref. Guyton & Hall 11th edition; page 629)

Decomposition of rhodopsin

When light energy is absorbed by rodopsin it decomposed to form prelumirodopsin. The prelumirodopsin converts to form lumirodopsin. This then decay to metarodopsin-I, metarodopsin-II and finally split to form all-transretinal and scotopsin.

Reformation of rodopsin : All-transretinal first reconvert to form 11-cis retinal catalyzed by retinal isomerase. This 11-cisretinal then combine with scotopsin to form rodopsin.

Dark adaptation

If a person spends a considerable length of time in brightly lighted surroundings and then moves to a dimly lighted environment, the retinas slowly become more sensitive to light as the individual becomes accustomed to the dark.

This decline in *visual threshold* is known as *dark adaptation*. It is nearly maximal in about 20 minutes, although there is some further decline over longer periods.

There are actually two components to the dark adaptation response :

a. The first drop in visual threshold, rapid but small in magnitude, is known to be due to dark adaptation of the cones.
b. In the peripheral portions of the retina, a further drop occurs as a result of adaptation of the rods.

The total change in threshold between the light-adapted and the fully dark-adapted eyes is very great.

The *time required for dark adaptation* is determined in part by the time required to build up the rhodopsin stores. In bright light, much of the pigment is continuously being broken down, and some time is required in dim light for accumulation of the amounts necessary for optimal rod function.

(Ref. Ganong 22th Edition; page166)

Light adaptation

On the other hand, when one passes suddenly from a dim to a brightly lighted environment, the light seems intensely and even uncomfortably bright until the eyes adapt to the increased illumination and the visual threshold rises.

This adaptation occurs over a period of about 5 minutes and is called *light adaptation*, although, strictly speaking, *it is merely the disappearance of dark adaptation.*

(Ref. Ganong 22th Edition; page166)

Deficiency sings of vitamin A

(Consequences of vitamin A deficiency) : In a word vitamin A deficiency produce *infection.*

1. ***Eye changes :*** Deficiency causes disintrigation of epithelium of cornea and lacrimal gland causes--
   a. Night blindness (nyctalopia) : This is the earliest change and is due to les formation of rhodopsin.

b. Xeropthalmia : Cojunctival kertinization.
c. Keratomalacia : Corneal softening and ulceration.
d. Bitot's sports : Triangular, shiny, gray (white plaques) spots on the conjunctiva.
e. Corneal scarring and blindness.

2. *Squamous metaplasia* : Squamous metaplasia of columnar mucus-secreting surfaces and transitional epithelium.
   Common sites are : Cornea, conjunctiva, upper respiratory tract, urinary tract, salivary gland, pancrease, sebaceous gland and sweat gland.
3. *Impaired immunity and increased susceptivity* to infections in childhood.

Reflexes of eye

Reflexes of eye are :

i. Light reflex
ii. Accomodation reaction
iii. Visual reflex.
iv. Conjuctival reflex
v. Lid closure reflex.

Direct & consentual light reflexes

If a light is shone (fall) into one eye, the pupils of both eyes normally constrict. The constriction of the pupil upon which the light is shone is called the *direct light reflex*; the constriction of the opposite pupil even though no light fell upon that eye is called the *consensnal light reflex.*

The afferent impulses travel through the optic nerve, optic chiasma, and optic tract. Here a small number of fibers leave the optic tract and synapse on nerve cells in the ***pretectal nucleus***, which lies close to the *superior colliculus*. The impulses are passed by axons of the pretectal nerve cells to the parasympathetic nuclei *(Edinger-Westphal nuclei)* of the third cranial nerve on *both sides*.

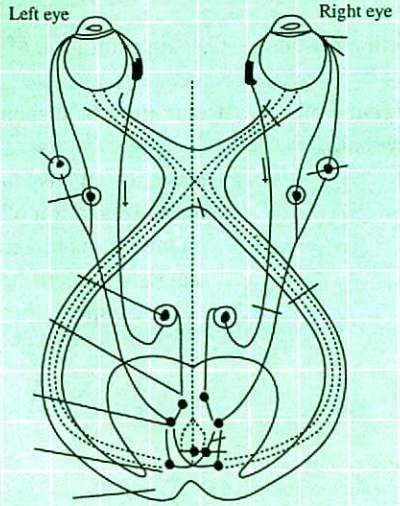


Fig. 17-7. Pathway of light reflex.

Here the fibers synapse and the parasympathetic nerves travel through the third cranial nerve to the cilliary ganglion in the orbit. Finally, postganglionic parasympathetic fibers pass through the short clliary nerves to the eyeball and the constrictor pupillae muscle of the iris.

Both pupils constrict in the consensual light reflex because the pretectal nucleus sends fibers to the parasympathetic nuclei on both sides of the midbrain. The fibers that cross the median plane do so close to the cerebral aqueduct in the posterior commissure.

(Clinical neuroanatomy 5th edition- R S. Snell; page 336)

Schematic representation of light reflex :

Fall of light on cornea
↓
Received by Rods and cones
↓
Optic nerve
↓
Optic tract
↓
Pretectal nucleus
↓
Edinger-westphal nucleus of both sides
↓
Occulomotor nerve
↓
Cilliary ganglion
↓
Short cilliary nerve
↓
Sphincter pupillae
↓
Constriction of the pupil.

Accomodation reaction

When the eyes are directed from a distant to a near object, contraction of the medial recti brings about convergence of the ocular axes; the lens thicken to increase its refractive power by contraction of the ciliary muscle; and the pupils constrict to restrict the light waves to the thickest central part of the lens.

The afferent impulses travel through the optic nerve, the optic chiasma, the optic tract, the lateral geniculate body, and the optic radiation to the *visual cortex*. The visual cortex is connected to the eye field of the ***frontal cortex***. From here-

i. Cortical fibers descend through the *internal capsule* to the *oculomotor nuclei* in the midbrain. The oculomotor nerve travels, to the medial recti muscles.

ii. Some of the descending cortical fibers synapse with the parasympathetic nuclei *(Edinger-Westphal nuclei)* of the third cranial nerve on *both sides*. Here the fibers synapse

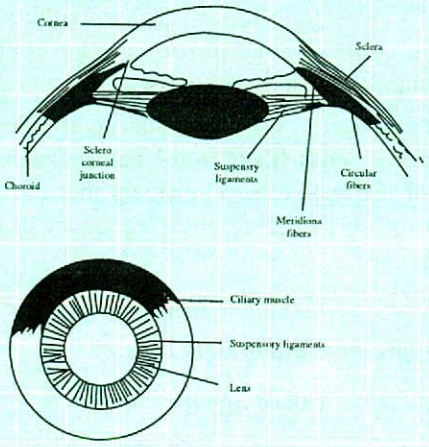


Fig. 17 - 8. *Mechenism of accomodation reaction.*

and the parasympathetic nerves travel through the occulomotor nerve to the ciliary ganglion in the orbit. Finally, postganglionic parasympathetic fibers pass through the short ciliary nerves to the *ciliary muscle* of the ciliary body and the *constrictor pupillae muscle* of the iris.

(Lens of eye lies within lens capsule. The capsule is suspended by suspensory ligament of which the other end is attached to the cilliary body. So, When cilliary muscle contract, the suspensory ligament relaxes. The relaxation of suspensory ligament causes relaxation of lens capsule. Due to this relaxtion of lens capsule the lens become more convex specially the anterior surface.)

(Clinical neuroanatomy 5th editison- R S. Snell; page 336)

In this reaction following changes occur :

1. Convergence of eye ball..
2. Modification of the shape of the lens i.e increase anterior-posterior diameter of the len; specially anterior surface (due to contraction of cilliary muscle → relaxation of suspensory ligament)

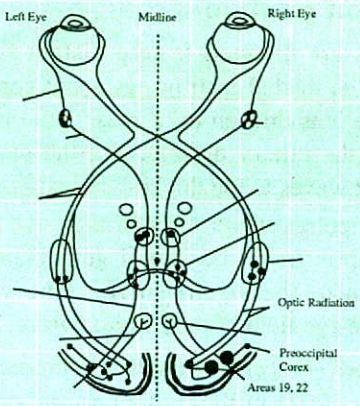


Fig. 17-9. *Pathway for the accomodation reaction.*

3. Constriction of pupil.

Structures involved in accomodation :

i. Cilliary muscle
ii. Suspensory ligament.
iii. Lens capsule
iv. Lens.
v. Iris.

Schematic representation of accomodation reaction

Light falling on cornea
↓
Rods and cones
↓
Optic nerve
↓
Optic tract
↓
Lateral geniculate body
↓
Optic radiation
↓
Visul cortex
↓
Superior longitudinal fasciculus
↓
Frontal eye field (frontal cortex)
↓
Through the internal capsule to the

↓	↓
Occulomotor nucleus	*Endinger westphal nucleus*
↓	↓
Occulomotor nerve	Ciliary ganglion
↓	↓
Contraction of the	Short ciliary nerve
↓	↓
medial rectus muscle	Causes contration of ciliary muscle
↓	↓
Convergence of the eyeball.	Relaxation of suspensory ligament
	↓
	Relaxation of suspensory ligament causes relaxation of lens capsule. Due to this relaxtion of lens capsule the lens become more convex specially the anterior surface.
	↓
	Helps to see the near objects.

Visual reflex

Sudden turning of the head, neck and upper part of the trunk towards a sudden flash of light is called visual reflex.

Pathway of visual reflex : Light falling on the cornea after traversing the refractive media of the eye ball stimulates the rods and cones of the retina → Optic nerve → Optic tract → Brachium of the superior colliculus →

i. Tectobulber tract → accessory nerve, supplying the muscles of the neek and head.
ii. Tectospinal tract → Anterior horn cells of the spinal cord, which supplies the muscles of the back concerned.

Visual pathway

Light falling on the cornea after traversing the refractive media

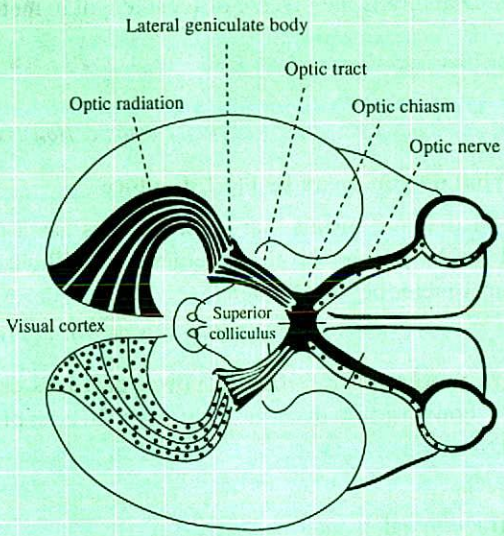


Fig. 17 - 10. *The visual Pathway.*

of the eye ball, stimulates the Rods and cones → Optic nerve → Optic tract → Lateral geniculate body → Optic radiation → visual cortex.

Effect of injury/lesion at different levels of visual pathway :

Site of injury	*Effect*
i. Optic nerve	Blindness of the affected eye.
ii. Crossed fibre	Bitemporal hemianopia.
iii. Uncrossed fibre	Binasal hemianopia.
iv. Optic tract	Homonymous hemianopia.

Corneal reflex

Light touching of the cornea or conjunctiva results in blinking of the eyelids. Afferent impulses from the cornea or conjunctiva travel through the ophthalmic division of the *trigeminal nerve* to the sensory nucleus of the trigeminal nerve. *Internuncial neurons* connect with the motor nucleus of the facial nerve on both sides through the *medial longitudinal fasciculus*. The *facial nerve* and its branches supply the *orbicularis oculi muscle*, which causes ***closure of the eyelids***.

(Clinical neuroanatomy 5th edition- R S. Snell; page 337)

Visual body reflexes

The automatic *scanning movements* of the eyes and head made when reading. The automatic movement of the eyes, head, and neck toward the source of the visual stimulus and the protective closing of the eyes and even the raising of the arm for protection are reflex actions that involve the following reflex arcs. The visual impulses follow the optic nerves, optic chiasma. and optic tracts to the *superior colliculi*. Here the impulses are relayed to the *tectospinal* and *tectobulbar* (tectonuclear) tracts and to the neurons of the *anterior gray* columns of the *spinal cord* and *cranial motor nuclei.*

(Clinical neuroanatomy 5th edition- R S. Snell; page 337)

Pupillary skin reflex

The pupil will dilate if the skin is painfully stimulated by pinching. The afferent sensory fibers are believed to have connections with the efferent preganglionic sympathetic neurons in the lateral gray columns of the first and second thoracic segments of the spinal cord. The *white rami communicantes* of these segments pass to the sympathetic trunk and the preganglionic fibers ascend to the superior *cervical sympathetic ganglion*. The postganglionic fibers pass through the *internal carotid plexus* and the long clilary nerves to the dilator pupillae muscle of the iris.

(Clinical neuroanatomy 5th edition- R S. Snell; page 338)

Argyll Robertson pupil

Definition : It is a condition in which light reflex is lost but accomodation is retained.

Cause :

1. Syphilitic degeneration of CNS.
2. Lesion close to the occulomotor nucleus so that pretectal fibre are affected.
3. Lesion of fibres from pretectal nucleus to Edinger westphal nucleus.

Binocular vision

Definition : The process of seeing one object by two eye is called binocular vision.

Visual sensation that is produced when the images fall on the symetrical points or corresponding points of each retina is called binocular vision. The central parts of the visual fields of the Iwo eyes coincide; therefore, anything in this portion of the field is viewed with binocular vision.

Coresponding points : The points on the retina on which the image of an object must fall if it is to be seen binocularly as a single object.

Condition for binocular vision :

1. Two visual field must overlape.
2. Similar image must form on two retina at similar points.

3. The coordinated movement of extra ocular muscles.

Advantage of binocular vision :

1. It provides accurate perception of depth, size and distance.
2. Optical defects of one eye is corrected by another.
3. The combined field of vision is wider than that of single eye.

Diplopia or Double vision

i. *Definition* : Seeing of an object as two is called double vision.

ii. *Cause* :

a. Derangements of extraocular muscles
b. Neurological disorders
c. Refractive error i.e. astigmatism
d. Incorrect spectacles
e. Media opacity i.e. cataract
f. Macular disease.

Focal point : Parallel light rays passing through the lens will bent and pass through a single point is called focal point.

Nodal point : Center of lens is called nodal point. The optical centre lies in the posterior part of the lens.

Optic axis : The line passing through the centre of curvature of cornea and the two surfaces of the lens, meets the retina at fovea centralis.

Anterior focal distance : It is about 15 mm in front of the cornea.

Posterior focal distance : It is about 24 mm in front of the cornea.

Principal axis : The light which pass through the nodal point without deviation is called principal axis.

Refraction : The bending of light rays at an angulated interface while passing from one media to another madia of different density, is called refraction.

(Ref. Guyton & Hall 11th edition)

Refractive index : The refractive index is a relative measure of transmission of light through a refracting surface in relation to the speed of light in the air.

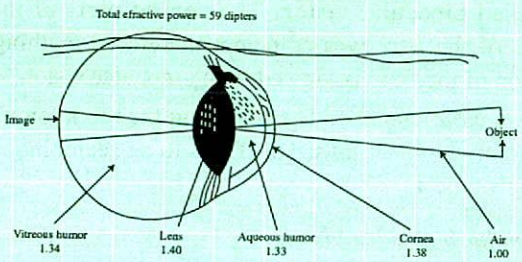


Fig. 17-3. *Refractive media with refractive index.*

Calculation : It is calculated as the velocity of light in air/ velocity of light in the medium concerned.

Example : Light passes through the lens of eye 214285 km/second

Light passes through the air 3,00000 km/second.

$$\text{So, Refractive index of lens} = \frac{300000}{214285}$$

$$= 1.4$$

(Refractive index of air is : 1.00*).*

Diaptores : Refracvtive power of lens is measured in terms of diaptores. Diaptore is the inverse of focal length in meter.

$$D \propto \frac{1}{f} \text{ m}$$

(Ref. Guyton & Hall 11th edition)

Q. 00. **What do you mean by (+) 1 diaptore***?*

Ans. (+) 1 diaptore means that a convex lens has a refractive power of (+) 1 diaptore and it converges parallel light rays to a focal point 1 meter beyond the lens.

(Ref. Guyton & Hall 11th edition)

Refractive power : The refractive power of a lens denotes its power to converge or diverge light rays. It is expressed as diapter (D).

It depends on -

a. Its refractive index and
b. Its radius of curvature.

Deffraction : Light rays passing along the edges of lens are bent. This bending of light are called deffraction. When light rays are allowed to pass through a small aperture, deffrafction takes place. As a result of deffraction, a point object will form dark and light rings which can be seen if is focussed on a screen.

Colour vision

Cones are responsible for color vision. Human are *trichromats* i.e. they have three cone pigments.

a. *Cone pigments are* :
   i. Short wave pigment : senses blue
   ii. Medium wave pigment : senses green
   iii. Long wave pigment : senses yellow and red.

b. *Cone systems in human retina* : Three cone systems in human retina give rise to three pigments :
   i. Blue sensitive or short wave pigment i.e *cyanolabe*
   ii. Green sensitive or medium wave pigment i.e *chlorolabe*
   iii. Red sensitive or long wave pigment i.e *erythrolabe.*

The sensation of any given color being determined by

relative frequencies of the impulses from each of these systems.

c. *Characteristics of color*
   i. Colors have three attributes : hue, intensity, and saturation i.e. degree of freedom from dilution with white.
   ii. For any colour there is a complementary colour that, when properly mixed with it, produces a sensation of white.
   iii. Black is the sensation produced by the absence of light, but it is probably a positive sensation, because the blind eye does *see black*, it sees nothing.

d. *Primary colors* : Primary colors are-
   i. Red
   ii. Green
   iii. Blue.
      * The sensation of white, any spectral color, and even the extraspectral color, purple, can be produced by mixing various proportions of red light, green light and blue light.
      * Red and blue are called the primary colors.

Young-Helmholtz theory

The sensation of color will depend on the extent to which each type of cones is excited to different color. This is called Young-Helmholtz theory.

e. *Mechanism of color vision* : Color is mediated by ganglionic cells that subtract or add input from one type of cone to input from another type. Processing in the ganglionic cells and lateral geniculate nucleus produces impulses that pass to the visual cortex. However, it is not known how visual cortex converts color input into the sensation at color.

   The sensation of any given color being determined by the relative frequencies of the impulses from each of three cone systems :
   a. *S pigment* i.e blue sensitive or short-wave pigment : Absorbs light maximally in the blue-violet portion of the spectrum.
   b. *M pigment* i.e green sensitive or medium-wave pigment : Absorbs light maximally in the green portion of the spectrum
   c. *L pigment* i.e red sensitive or long-wave pigment : absorbs light maximally in the yellow portion of the spectrum and also sensitive enough in the red portion.

Colour blindness

The suffix- *anomaly* denotes colour weakness and the suffix *anopia*- color blindness.

The prefix *prot*-, *deuter*-, and *tri*- refer to defects of the red, green, and blue cone systems respectively.

i. *Colour weakness are* :
   a. *Trichromats* : Individuals with normal color vision and all three cone system, but one may be weak.
   b. *Dichromats* : Individuals with two cone systems. They may have protanopia, deuteranopia, or tritanopia.
   c. *Monochromats* : Individuals with only one cone system.

ii. Types of colour blindness :
   a. *Protanopia* : Lack of red color sensation
   b. *Deuteranopia* : Lack of green color sensation
   c. *Tritanopia* : Lack of blue color sensation

iii. Causes of color blindness include:
   a. Inherited
   b. Lesion in visual cortex i.e area V8
   c. Drugs : Sildenafil (Viagra) causes transient blue-green color weakness because this drug inhibits the phosphodiesterase of retina.

iv. *Inheritance of colour blindness* : Color blindness is a sex linked (i.e. X-linked recessive) disorder resulting from the absence of the appropriate color genes on the X chromosome or X chromosomes contain abnormal gene.
   a. Male have only one X chromosome, but female have two X chromosomes. Therefore colour blindness mostly occurs in male.
   b. Female only shows when both X chromosomes are defective.
   c. Female child of a man with X-linked color blindness are carriers of colour blindness and pass to defects on to half of their sons.
   d. X-linked color blindness skips generations and appears in males of every second generation.

Types of eye

i. ***Emmetropia*** : It is the normal optical condition. The eye is considered to be emmetropic when incident parallel rays of light from infinity come to a focus on the retina *(fovea centralis)* with accommodation at rest.
   a. There is no error of refraction. An emmetropic eye will have a clear image of a distant object without any internal adjustment of its optics.
   b. The average power of a normal emmetropic eye is +58 to +60 D (diaptor).
   c. Most emmetropic eyes are approximately 24 mm in length.

Defect of vision

It is usually of two types :
i. Refractive errors
ii. Normal aberrations.

Refractive errors : There are 4 refractive errors

1. Myopia or short sightness
2. Hypermeteropia
3. Astigmatism
4. Presbiopia.

Normal aberration :

a. *Spherical aberration* : The peripheral rays in a convex lens are focussed at a nearer point than the central rays. So, that the margins of immage become blurred. This is called spherical aberration.

Correction : In normal eye it is corrected in two ways-

i. The iris shuts off the peripheral rays.

ii. The refractive power of the central part of lens is higher than peripheral.

b. *Chronic aberration* : Due to different wave lengths, light of different colour undergo different degree of refraction. (Red light refracted least; violet light refracted most). Hence the margin of the image may show rain bow colour. This is called chronic aberration.

Correction : It is normally rectified in two ways -

i. The difference of refractive power of the various refractive media of eye ball partly correct it.

ii. The colour fringes are ignored by the brain.

Errors of refraction *(ametropia)*

The optical condition of the eye in which the incident parallel rays of light do not come to a focus upon the light sensitive layer of the retina, with accommodation at rest is known as *ametropia*.

Etiology :

i. Axial ametropia : There is abnormal length of the eyeball.
   a. Too long : In myopia
   b. Too short : In hypermetropia

ii. Curvature ametropia There is abnormal curvature of the refracting surfaces of the cornea or lens.
   a. Too strong : In Myopia
   b. Too weak : In hypermetropia

iii. Index ametropia : There is abnormal refractive index of the media.
   a. Too high : In myopia
   b. Too low : In hypermetropia.

iv. Abnormal position of the lens :
   a. Forward displacement : In myopia
   b. Backwanl displacement : In hypermetropia.

Myopia (short sight)

It is that dioptric condition of the eye in which with the accommodation at rest, incident parallel rays of light come to a focus anterior to the light sensitive layer of retina.

Etiology :

a. It is basically a disturbance of growth on which degenerative changes are superimposed.

b. The part anterior to the equator is normal.

c. The increase in axial length affects the posterior pole and the surrounding area.
   i. *Axial* : Increased anteroposterior diameter of the globe is the most common cause.
   ii. *Curvature* : Increased curvature is seen in following conditions :
      Corneal : Conical cornea. ectasia
      Lens : Lenticonus.
   iii. *Index* : Increased refractive index of the nucleus as in senile nuclear cataract.
   iv. *Forward displacement of the lens*, e.g as in anterior dislocation of the lens.

Tpes of myopia :

i. Congenital (developmental myopia)
ii. Simple myopia
iii. Pathological

Signs of myopia :

i. Prominent eyes, large pupil and deep anterior chamber are commonly seen.
ii. Apparant divergent squint may be present

Complications of myopia :

i. Vitreous degeneration (liquefaction), opacities and detachment are commonly seen.
ii. Tear and haemorrhages occur in the retina due to chorioretinal degeneration.
iii. Retinal detachment (simple) is always due to break in the retina through which fluid seeps in, raising the retina from its bed.
iv. Complicated cataract (posterior cortical) is due to the disturbance to the nutrition of the lens.
v. High myopia is sometimes associated with chronic simple glaucoma.

Treatment :

i. Spectacles : By spherical concave lens.
ii. Hygiene of eyes : Proper position, good illumination and

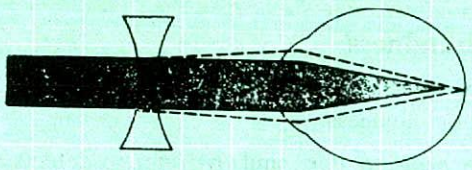


Fig. 17-4. *Corrction of Myopia.*

correct distance from the book (about 25 cm) while reading is essential.

iii. Operative :
   a. Radial keratotomy
   b. Excimer laser
   c. Epikeratophakia
   d. Keratomileusis
   e. LASIK (Laser-assisted in situ keratomileusis) : It corrects myopia of -8 to -16.

Hypermetropia (Far sight)

It is that dioptric condition of the eye in which with the accommodation at rest the incident parallel rays of light come to a focus posterior to the light sensitive layer of the retina.

Incidence : Newborns are invariably hypermetropic (average 2.5 D). The incidence decreases rapidly with age remaining at about 50% after 20 years.

Etiology :

i. Axial : There is short length of the eyehall.
ii. Curvature : There is flat carvature of the cornea.
iii. Index : There is increase in refractive index of the cortex, e.g. as in diabetic and senile cortical cataracts.
iv. Backward displacement of the lens as in posterior dislocation of the lens.
v. Absence of lens or aphakia

Types of hypermetropia :

i. *Latent hypermetropia* : It is overcome by the normal tone of the ciliary muscle. It is detected only when the ciliary muscle is paralysed by atropine.
ii. *Manifest hypermetropia* : It is detected without paralysing the ciliary muscle.
   a. *Facultative* : It can be overcome by an effort of accommodation.
   b. *Absolute* : It cannot be overcome by an effort of accommodation.

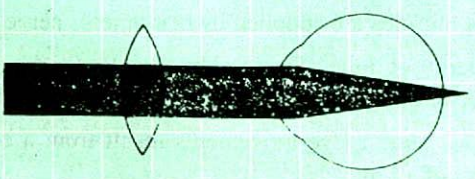


Fig. 17-5. *Correction of hypermetropia.*

Treatment : It is treated by prescribing suitable correcting spherical convex lenses.

Astigmatism

It is that condition of refraction in which a point of light cannot be made to produce a punctatc image upon the retina by any spherical correcting lens (astigmatism = a point).

Etiology :

i. There is unequal curvature of the cornea in difierent meridian.
ii. There is decentring of the lens, e.g. as in subluxation of lens.

Types :

i. Regular
   a. Simple
   b. Compound
   c. Mixed
ii. Irregular.

Treatment :

i. If there are no symptoms, no treatment is required in low degree of astigmatism
ii. When there are symptoms, suitable cylindrical lenses are prescribed for constant use.

Presbiopia

Fall of immage behind the retina due to defect or failure in accmodation. In this condition the person fell difficulty for viewing near vision due to failure in accommodation.

Correction : By using convex lens.

Visual acuity

Visual acuity is the degree to which the details and contours of objects are perceived. Although there is evidence that other measures are more accurate, visual acuity is usually defined in terms of the minimum separable- ie, *the shortest distance by which two lines can be separated and still be perceived as two lines.*

Clinically, visual acuity is often determined by the use of the familiar Snellen letter charts viewed at a distance of 20 ft (6 m). The individual being tested reads aloud the smallest line distinguishable.

The results are expressed as a fraction :

i. Numerator : The numerator of the fraction is 20, the distance at which the subject reads the chart.
ii. Denominator : The denominator is the greatest distance from the chart at which a normal individual can read the smallest line the subject can read.

Normal visual acuity is 20/20; a subject with 20/15 visual acuity has better than normal vision (not farsightedness); and one with 20/100 visual acuity has subnormal vision.

The *Snellen charts* are designed so that the height of the letters in the smallest line a normal individual can read at 20 ft subtends a visual angle of 5 minutes. Each of the lines in the letters are separated by 1 minute of arc. Thus, the minimum separable in a normal individual corresponds to a visual angle of about 1 minute.

Factors affecting visual acuity :

i. Image-forming mechanisms of the eye
ii. Retinal factors such as the state of the cones
iii. Stimulus factors including-
   a. Illumination
   b. Brightness of the stimulus
   c. Contrast between the stimulus and the background
   d. Length of time the subject is exposed to the stimulus.

(Ref. Ganong 22th Edition; page167)

N. B.

a. Normal VA : 6/6
b. Subnormal VA : 6/9
c. Visual acuity 6/12 means, that a person sees at 6 m what the normal eye could see at 12 m.
d. Visual acuity needed for driving: 6/9 - 6/12
e. Visual acuity < 1/60 is legal blindness.
f. Visual acuity 3/60 indicates that the individual can not see the line at 3 meters which a normally sighted person could read at 60 meters.

Importance of visual acuity : It helps in determining shape, form outline and minute details of sunoundings.

Visual fields

The visual field of each eye is the portion of the external world visible out of that eye. The normal field extends 160° horizontally and 130° vertically with a blind spot 15° from fixation in the temporal field.

Lens causes the image on the retina to be inverted. Thus an object in the lower part of the visual field is projected to the upper retina and an object in the temporal half of the visual field is projected to the nasal half of the retina.

a. *Visual field in each eye is named as* :
   i. Nasal field of vision i.e superior and inferior quadrant of nasal side.
   ii. Temporal field of vision i.e superior and inferior quadrant of temporal side.
b. *Decussation fibers* :
   i. The fibers from the nasal half of each retina decussate in the optic chiasma.
   ii. The optic tract conntains fibres from the temporal half of one retina and nasal half of the other i.e optic tract subserves half of the field of vision.

Visual field defects

Visual field defects are termed as :

i. *Homonymous hemianopia* : Same side of the both visual field defects (half blindness).
   Example : In right half of visual field defect nasal field of left eye is affected, and temporal feld of right eye is affected.
ii. *Heteronymous hemianopia* : Opposite side of the both visual field defects (half blindness).

Perimetry

Visual fields are mapped with an instrument called perimeter and the process is referred to as peirmetry.

Eye movement

Since much of the visual field is binocular, it is clear that a very order of coordination of the movements of the two eyes is necessary if visual images are to fall at all times on corresponding points in the retinas and diplopia is to be avoided.

i. Types : There are four types of eye movements :
   a. *Saccades* : Sudden jerky movements, occurs as the gaze shifts from one object to another.
   b. *Smooth pursuit movements* : Tracking movements of the eyes as they follow moving objects.
   c. *Vestibular movements* : Adjustments that occur in response to stimuli initiated in the semicircular canals, maintains visual fixation as the head moves.
   d. *Convergence movements* : Movements that bring the visual axes towards each other as attention is focused on objects near the observer.

   Saccadic movements seek out visual targets; pursuit movements follow them as they move about; and vestibular movements stabilize the tracking device i.e the head.

ii. *Muscles involved* : Six muscles (extraocular muscles) control eye movements :
   a. Superior rectus
   b. Inferior rectus
   c. Medial rectus
   d. Lateral rectus

   These 4 muscles are supplied by oculomotor nerve (3rd)

   e. Superior oblique : Supplied by trochlear nerve (SO4)
   f. Inferior oblique : Supplied by abducens nerve (LR6).

ii. *Eye movements* : Eye movements result from a continuous interplay of all muscles.
   a. Superior rectus : Rotates the eyeball upwards
   b. Inferior rectus : Rotates the eyeball downward
   c. Medial rectus : Rotates the eyeball inward
   d. Lateral rectus : Rotates the eyeball outward

   These 4 muscles are supplied by oculomotor nerve (3rd)

e. Superior oblique : Rotates the eyeball so that cornea turns in a downward and outward directions.
f. Inferior oblique : Rotates the eyeball so that the cornea turns upwards and outward.

Q. 00. **What is the effect of sympathetic and parasympathetic stimulation on pupil?**

i. Sympathetic : Dilatation of pupil *(mydriasis)* due to contraction of radial muscle of iris.
ii. Parasympathetic : Constriction of pupil *(miosis)* due to contraction of circular muscte of iris.

Q. 00. **What is the function of conjunctiva?**

Ans. Protection and lubrication of eye.

Q. 00. **How aqueous humour is formed?**

Ans. The cilliary body produces aqueous humour by diffusion and active transport process.

Q. 00. **What is intraocular pressure?**

Ans. Intraocular pressure :

i. *Definition* : Intraocular pressure is the pressure inside the eyeball.
ii. *Normal values* : It is about 16 mmHg in normal eye (range : 12 - 20 mmHG).
iii. Importance : lOP is increased in glaucoma.

Strabismus /Squint

When the axes of the eyes are not equal the visual images no longer fall on corresponiing points, and strabismus (squint) is said to be present.

Applied

Q. 00. **Write short notes on- Miosis.**

Ans. Miosis :

I. *Definition* : The pupil is small and constricted due to the action of sphincter pupillae muscle.
II. *Etiology* :
   a. Physiological : Babies, old age, blue eyes.
   b. Pharmacological :
      i. Local : Miotic i.e. pilocarpine
      ii. Systemic : Morphin.
   c. Pathological :
      i. Unilateral : Acute iritis i.e. Healed iritis, Horner's syndrome.
      ii. Bilateral : Pontine haemorrhage, Argyll-Robertson pupil.

Q. 00. **Write short notes on- Mydriasis.**

I. *Definition* : The pupil is dilated due to the action of dilator pupillae muscle.
II. *Etiology* :
   a. *Physiological* : Myopia, nervous excitement.
   b. *Pharmacological* : Mydriatics i.e. atropine, phenylephrine, cyclopentolate, tropicamide,.
   c. *Pathological* :
      i. *Retina and optic nerve diseases* : Optic nerve atrophy, absolute glucoma, acute congestive glucoma,
      ii. *Central lesion* (above lateral geniculate body) : Meningitis, haemorrhage, uraemia.
      iii. *Oculomotor nerve paralysis* : Trauma, syphilis, diphtheria, meningitis.
      iv. *Irritation of cervical sympathetics* : Apical pneumonia, pleurisy, cervical rib.

Q. 00. **Write short notes on- Aphakic eye.**

Ans. Aphakic eye :

i. *Definition* : Aphakia is a condition of the eye where lens has been been removed i.e. absence of lens. It is a classical example of acquired high hypermetropia.
ii. *Optical condition* :
   a. The eye is hypermetropic
   b. There is loss of accommodation
   c. The retinal image is about 25% larger.
   d. Astigmatism (against the rule) : The surgical scar at the corneoscleral junction in the upper part ot the cornea flattens the vertical meridian of the cornea.
iii. *Symptom* : There is gross dimness of vision because of acquired high hypermetropia.
iv. *Signs* :
   a. A linear semicircular corneo-scleral scar mark is seen in the upper half of cornea.
   b. The iris shows peripheral buttonhole iridectomy at or near 12 O'clock position.
   c. The anterior chamber is deep due to lack of support of the iris by the lens.
   d. There is often iridodonesis or tremulousness of the iris due to lack of support.
   e. The pupil is jet black.
v. *Correction* :
   a. By spectacles : Spherical convex lens (+ 10 D approximately).
   b. Contact lens.
   c. Introcular lens implantation (IOL).

Taste

Taste is mainly a function of the taste buds in the mouth, but it is common experience that one's sense of smell also contributes strongly to taste perception.

Importance of taste : Taste allows a person to select food in accord with desire and perhaps also in accord with the needs of the tissues for specific nutritive subatances.

(Ref. Guyton & Hall 11th edition)

Primary taste sensation or basic taste modalities

On the basis of physiological studies, there are generally steaded to be four primary sensations of taste.

1. Sour taste : is caused by acid
2. Salty taste : is elicited by ionized salts.
3. Sweet taste : is caused by sugars, gly-cols, alcohols, aldehydes, Ketones, ami-des, esters, amino-acids, sulfuric acids, halogina-ted acids and inorganic salts of lead and beryllium.

   Saccrine - can be used as sweeting agent. It is more than 600 times as sweet as common table sugar, and since it is not toxic (except that it might be mildly carcinogenic).
4. *Bitter* taste : Two particular classes of substance are specially likely to cause bitter test sensation-
   a. Long chain organic susbstances containing nitrogen.
   b. Alkaloids : include many of the drugs used in medicines such as quinine, caf-feine, strychnine and nicotin.

(Ref. Guyton & Hall 11th edition)

Taste blindness

Many persons are taste blind for certain substances, especially for different types of thiourea compounds. A substance used frequently by psychologists for demonstrating taste blindness is phenyl thiocarbamide, for which approximately 15 to 30 percent of all people. exhibit taste blindness, the exact percentage depanding on the method of tasting and the concentration of the substance. *(Ref. Guyton & Hall 11th edition)*

Location of the taste bud

Taste buds for :

1. The *sweet* and *salty* taste : are located principally on the tip of the tongue.
2. The *sour* taste : on the two lateral sides of the tongue.
3. The *bitter* taste : on the circumvallate papillae on the posterior tongue.

(Ref. Guyton & Hall 11th edition)

Taste bud

i. *Definition* : Taste buds are the sense organ for taste.
ii. *Shape* : Ovoid
iii. *Diameter* : 50-70 μm
iv. *Length* : 1/16 millimeter
v. *Diameter* : 1/30 millimeter
v. *Total number* : About 10,000.
vi. *Situation* :
   a. In the wall of the fungiform and vallate papillae of the tongue.
   b. Mucosa of the epiglotis, palate, and pharynx.
vii. *Location* : Taste buds for the-
   a. *Sweet and salty* : on the tip of the tongue.
   b. *Sour* : on the two lateral sides of the tongue.
   c. *Bitter taste* : on the circumvallate papillae on the posterior tongue.
vii. *Innervation* : Each taste bud is innervated by about 50 nerve fibres and consequently each nerve fibre receives input from an average of five taste buds.
vi. *Composition* :
   i. About 40 modified epithelial cell, some of which are supporting cells called sustenti-cular cells and others are taste cells.
   ii. Inter woven among the taste cells is a branching terminal net work of several taste nerve fibres that are stimulated by the taste cells.
vii. *Replacement* : The taste cells are continualy being replaced by mitotic division from the surrounding epithelial cells so that some are young cells and others are mature cells that lie toward the centre of the bud and soon dissolute.
viii. *Pores* : The outer tips of the taste cells are arranged around a minute pore. From the tip of each cell, several micro villi or taste hairs, about 2 to 3 mic rons in length and 0·1 to 0·2 micron in width prorude outward into the taste pore to approach the cavity of the mouth.

   These microul are beleived to provide the receptor surface for taste.
ix. *Degereration* : An interesting features of the taste buds is that they completly degenerate when the taste nerve fibres are destroyed.

(Ref. Guyton & Hall 11th edition)

N. B. *Other information* : The taste cells are continualy being replaced by mitotic division from the surrounding epithelial cells so that some are young cells and others are mature cells that lie toward the centre of the bud and soon dissolute.

The outer tips of the taste cells are arranged around a minute pore. From the tip of each cell, several micro villi or taste hairs, about 2 to 3 microns in length and 0·1 to 0·2 micron in width prorude outward into the taste pore to approach the cavity of the mouth.

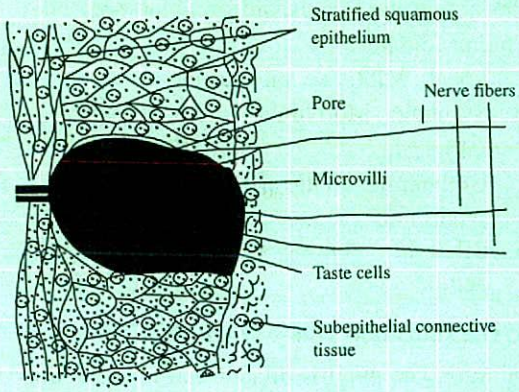


Fig. 17-12. *The taste bud*

These microul are beleived to provide the receptor surface for taste.
An interesting features of the ta ste buds is that they completly degenerate when the taste nerve fibres are destroyed.

(Ref. Guyton & Hall 11th edition and others)

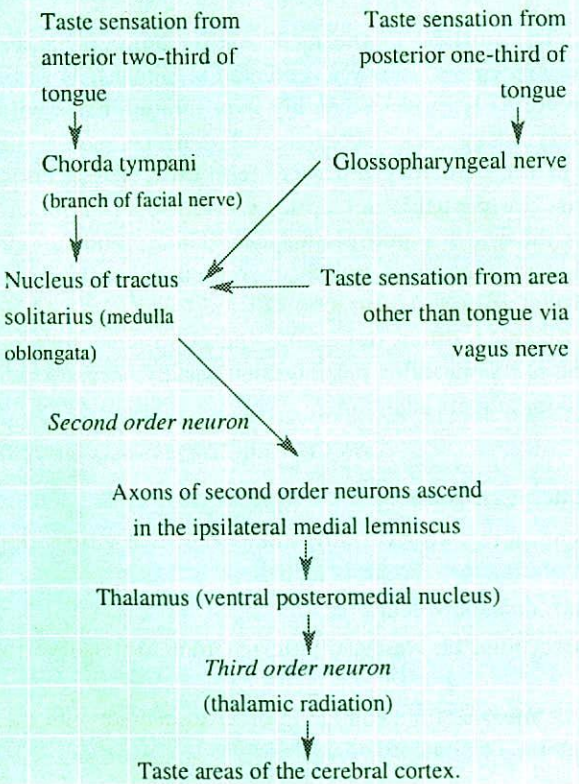
Transmission of taste signals *(in the central nervous system)* :

Taste impulses from the anterior two thirds of the tongue pass first into the fifth nerve and then through the chorda tympani into the facial nerve, thence into the tractus solitarius in the brain steam. Taste sensation from the circumvallate papillae on the back of the tongue and from the other posterior regions of the mouth are trans-mitted through the glossopharyn-geal nerve also into the tractus solitarius but at a slightly lower level. A few taste singnals are transmitted into the tractus solitarius from the base of the tongue and other parts of the pharyngeal region by way of the vagus nerve.

All taste fibres synapse in the nuclei of the tractus solitarius and send second order neurone to the thalamus. From the thalamus third order neurons are transmitted to the lower tip of the post central gyrus in the parietal cortex. Where it curls deep into the sylvian fissure. Third order neurons also project to the near by opercular- insular area.

Q. 00. Trace the pathway of taste sensation.

Ans. Pathway of taste sensation :



Q. 00. **Describe the pathway of taste sensation.**

Ans. Transmission of taste signals *(in the central nervous system)* :

i. *Taste impulses from the anterior two thirds of the tongue* : pass first into the fifth cranial nerve and then through the chorda tympani into the facial nerve, thence into the tractus solitarius in the brain steam.

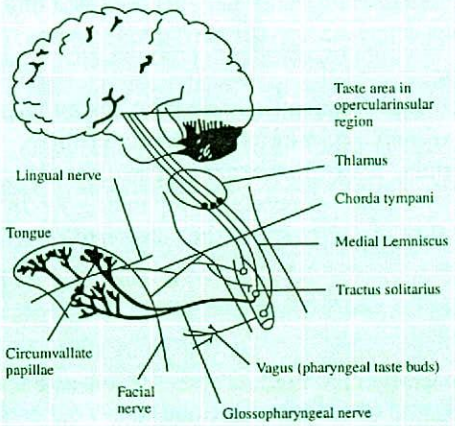


Fig. 17-13. *Transmission of taste signals in the the central nervous system.*

ii. *Taste sensation from the circumvallate papillae on the back of the tongue and from the other posterior regions of the mouth* : are transmitted through the glossopharyngeal nerve also into the tractus solitarius but at a slightly lower level.

iii. A few taste singnals are transmitted into the tractus solitarius from the *base of the tongue and other parts of the pharyngeal region* by way of the vagus nerve.

All taste fibres synapse in the nuclei of the tractus solitarius and send *second order neurone* to the thalamus. From the thalamus *third order neurons* are transmitted to the lower tip of the post central gyrus in the parietal cortex. Where it curls deep into the sylvian fissure. Third order neurons also project to the near by opercular-insular area.

(Ref. Guyton & Hall 11th edition)

Taste reflexes

From the tractus solitarius a large number of impulses are transmitted directly into the superior and inferior salvatory nuclei and these inturn transmit impulses to the submandibular, sublingual and parotid glands to help control the secretion of saliva during the ingestion of food.

(Ref. Guyton & Hall 11th edition)

Abnormalities of taste

i. *Ageusia* : Absence of the sense of taste

ii. *Hypogeusia* : Diminished taste sensitivity. Many different diseases can produce hypogeusia. In addition, drugs such as captopril and penicillamine, which contain sulfhydryl groups, cause temporary loss of taste sensation.

iii. Dysgeusia : Disturbed sense of taste.

(Ref. Ganong 22th Edition; page 188)

Applied

Q. 00. **What is taste blindness?**

Ans. *Taste blindness* : Many persons are taste blind for certain substances, especially for different types of thiourea compounds.

A substance used frequently by psychologists for demonstrating taste blindness is phenyl thiocarbamide, for which approximately 15 to 30 percent of all people exhibit taste blindness, the exact percentage depanding on the method of tasting and the concentration of the substance.

(Ref. Guyton & Hall 11th edition)

Smell

Smell is generally classified as visceral senses because of their close association with gastrointestinal function.

i. *Smell receptors* : are chemoreceptors that are stimulated by molecules in solution in mucus in the nose. The smell receptors are distance receptors (*teleceptors*), and the smell pathways have no relay in the thalamus.

Location : In a specialized portion of the nasal mucosa, the yellowish-pigmented olfactory mucous membrane it covers an area of 5 cm^2 in the roof of the nasal cavity near the septum.

ii. *Olfactory mucous membrane* : It contains supporting cells and *progenitor cells* for the olfactory receptors. Interspersed between these cells are 10-20 million receptor cells. Each olfactory receptor is a neuron, and the olfactory mucous membrane is said to be the place in the body where the nervous system is closest to the external world.

The olfactory mucous membrane is constantly covered by mucus. This mucus is produced by Bowman's glands, which are just under the basal lamina of the membrane.

iii. *Olfactory neurons* : Each neuron has a short, thick dendrite with an expanded end called an *olfactory rod*. From these rods, cilia project to the surface of the mucus. The cilia are unmyelinated processes about 2 μg long and 0.1 μm in diameter. There are 10-20 cilia per receptor neuron.

Axons : The axons of the olfactory receptor neurons pierce the cribriform plate of the ethmoid bone and enter the olfactory bulbs.

The olfactory neurons, like the taste receptor cells but unlike most other neurons, are *constantly being replaced* with a half-time of a few weeks. The olfactory renewal process is carefully regulated, and there is evidence that in this situation, a bone morphogenic protein (BMP) exerts an inhibitory effect.

iv. *Olfactory bulbs* : In the olfactory bulbs, the axons of the receptors contact the primary dendrites of the *mitral cells* and *tufted cells* to form the complex globular synapses called *olfactory glomeruli.*

Olfactory bulbs contain *periglomerular cells*, which are inhibitory neurons connecting one glomerulus to another, and *granule cells*, which have no axons and make reciprocal synapses with the lateral dendrites of the mitral and tufted cells. At these synapses, the mitral or tufted cell excites the granule cell by releasing glutamate, and the granule cell side of the synapse in turn inhibits the mitral or tufted cell by releasing GABA.

v. *Olfactory cortex* : The axons of the *mitral* and *tufted* cells pass posteriorly through the intermediate olfactory stria and the lateral olfactory stria to the olfactory cortex.

The axons terminate on the apical dendrites of pyramidal cells in the olfactory cortex. In humans, sniffing activates the piriform cortex, but smells with or without sniffng activate the lateral and anterior orbitofrontal gyri of the frontal lobe. The orbitofrontal activation is generally greater on the right side than the left. Thus, the cortical representation of olfaction is asymmetric. Other fibers project to the amygdala, which is probably involved with the emotional responses to olfactory stimuli, and to the entorhinal cortex, which is concerned with olfactory memories.

(Ref. Ganong 22th Edition; page 185, 186)

Sniffing : The portion of the nasal cavity containing the olfactory receptors is poorly ventilated in humans. Most of the air normally moves smoothly over the turbinates with each respiratory cycle, although eddy currents pass some air over the olfactory mucous membrane. These eddy currents are probably set up by convection as cool air strikes the warm mucosal surfaces. The amount of air reaching this region is greatly increased by sniffing, an action that includes contraction of the lower part of the nares on the septum, deflecting the airstream upward. Sniffing is a semi-reflex response that usually occurs when a new odor attracts attention.

(Ref. Ganong 22th Edition; page-188)

Odor producing substances

Physical characteristics of substances that can cause the stimulation of olfactory receptors include :

i. Substance must be volatile
ii. Substance must be water-soluble in order to dissolve in mucus
iii. Substance must be lipid soluble in order to interact with the lipid material of olfactory cilia.

Primary olfactory stimulant

i. Camporaceous
ii. Musky
iii. Floral
iv. Pepperminty

v. Etherea
vi. Putrid.

Pathway of olfaction :

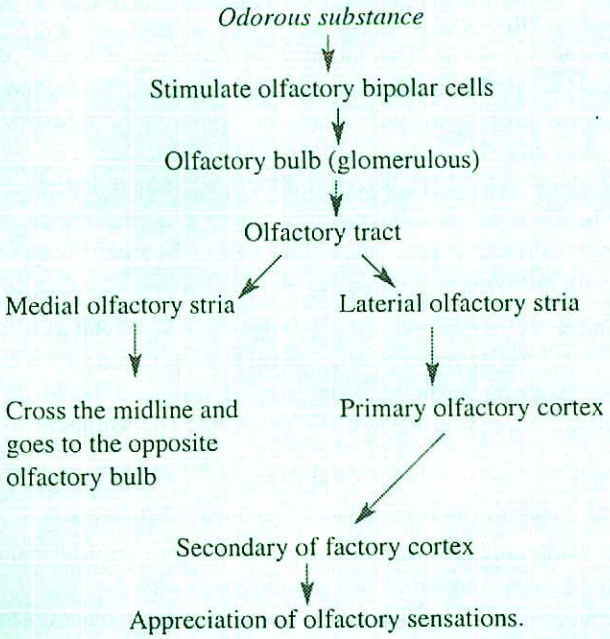
In contrast to all other sensory pathways, the olfactory afferent pathway has only two neurons and reaches the cerebral cortex without synapsing in one of the thalamic nuclei.

Olfactory receptors cells with one type of odorant receptor project to one olfactory glomerulous and olfactory receptors cells with another type of odorant receptor project to a different olfactory glomerulous.

i. First order neuron : bipolar cells of olfactory mucosa
ii. Second order neuron : mitral and tufted cells in the olfactory bulb.

The synapse occurs between these two neurons in the glomerulus of the olfactory bulb. The axons of the mitral and tufted cells form olfactory tracts which go to the opposite olfactory bulb and primary olfactory cortex.

Q. 00. **Trace the pathway of olfaction.**



Abnormalities of olfaction : Abnormalities of olfaction include-

a. *Anosmia* : Absence of the sense of smell. Several dozen different anosmias have been detected in humans. They are presumably due in each case to absence or disrupted function of one of the many members of the odorant receptor family.
b. *Hyposmia* : Diminished olfactory sensitivity
c. Dysosmia : Distorted sense of smell.

Olfactory thresholds increase with advancing age, and more than 75% of humans over the age of 80 have an impaired ability to identify smells.

(Ref. Ganong 22th Edition; page-191)

Hearing and Equilibrium

Introduction : Receptors for two sensory modalities, hearing and equilibrium, are housed in the ear.

a. *Hearing apparatus* :
   i. External ear
   ii. Middle ear
   iii. Cochlea of the inner ear.
b. *Equilibrium apparatus* :
   i. Semicircular canals
   ii. Utricle
   iii. Saccule of the inner ear.
c. *Receptors of hearing and equilibrium* : The receptors for hearing and equilibrium are hair cells, and there are six groups of hair cells in each inner ear :
   i One in each of the three semicircular canals
   ii. One in the utricle
   iii. One in the saccule
   iv. One in the cochlea.

   Function :
   i. Receptors in the semicircular canals detect rotational acceleration.
   ii. Receptors in the utricle detect linear acceleration in the horizontal direction.
   iii. Receptors in the saccule detect linear acceleration in the vertical direction.

(Ref. Ganong 22th Edition; page-171)

Anatomical considerations

a. ***External ear*** : The external ear funnels sound waves to the external auditory meatus. From the meatus, the external auditory canal passes inward to the tympanic membrane (eardrum).

(Ref. Ganong 22th Edition; page-171)

b. ***Middle ear*** : The middle ear is an air-filled cavity in the temporal bone that opens via the auditory (*eustachian*) tube into the nasopharynx and through the nasopharynx to the exterior. The tube is usually closed, but during swallowing, chewing, and yawning it opens, keeping the air pressure on the two sides of the eardrum equalized.

Auditory ossicles : The three auditory ossicles are in the middle ear :
i. Malleus
ii. Incus
iii. Stapes.

The *manubrium* (handle of the malleus) is attached to the back of the tympanic membrane. Its head is attached to the wall of the middle ear, and its short process is attached to the incus, which in turn articulates with the head of the

stapes. The stapes is named for its resemblance to a stirrup. Its foot plate is attached by an annular ligament to the walls of the oval window.

Skeletal muscles : Two small skeletal muscles, the *tensor tympani* and the *stapedius*, are also located in the middle ear. Contraction of the former pulls the manubrium of the malleus medially and decreases the vibrations of the tympanic membrane; contraction of the latter pulls the footplate of the stapes out of the oval window.

(Ref. Ganong 22th Edition; page-171)

c. ***Inner ear*** : The inner ear (*labyrinth*) is made of two parts, one within the other.

i. *Bony labyrinth* : The bony labyrinth is a series of channels in the petrous portion of the temporal bone. Inside these channels, surrounded by a fluid called *perilymph*, is the membranous labyrinth.

ii. *Membranous labyrinth* : This membranous structure more or less duplicates the shape of the bony channels. It is filled with a fluid called *endolymph*, and there is no communication between the spaces filled with endolymph and those filled with perilymph.

(Ref. Ganong 22th Edition; page-171)

d. ***Cochlea*** :

i. Coiled tube

ii. Length : 35 mm long and makes 23/4 turns.

iii. Throughout its length, the basilar membrane and Reissner's membrane divide it into three chambers (scalae).

The upper *scala vestibuli* and the lower *scala tympani* contain perilymph and communicate with each other at the apex of the cochlea through a small opening called the *helicotrema*. At the base of the cochlea, the scala vestibuli ends at the oval window, which is closed by the footplate of the stapes. The scala tympani ends at the round window, a foramen on the medial wall of the middle ear that is closed by the flexible secondary tympanic membrane. The scala media, the middle cochlear chamber, is continuous with the membranous labyrinth and does not communicate with the other two scalae. It contains endolymph.

(Ref. Ganong 22th Edition; page-171)

e. ***Organ of Corti*** :

i. *Location* : Located on the basilar membrane

ii. *Content* : *Hair cells* which are the auditory receptors.

The hair cells are arranged in four rows : *three rows of outer hair cells* (20,000) lateral to the tunnel formed by the rods of Corti, and *one row of inner hair cells* (3500) medial to the tunnel.

iii. *Afferent neurons* : The cell bodies of the afferent neurons that arborize around the bases of the hair cells are located in the spiral ganglion within the modiolus, the bony core around which the cochlea is wound.

90% to 95% of these afferent neurons innervate the inner hair cells; only 5-10% innervate the more numerous outer hair cells, and each neuron innervates several of these outer cells.

iv. *Efferent fibers* : By contrast, most of the efferent fibers in the auditory nerve terminate on the outer hair cells rather than on the inner hair cells. The axons of the afferent neurons that innervate the hair cells form the auditory (cochlear) division of the *vestibulocochlear acoustic nerve* and *terminate* in the dorsal and ventral cochlear nuclei of the *medulla oblongata*.

The total number of afferent and efferent fibers in each auditory nerve is approximately 28,000.

(Ref. Ganong 22th Edition; page-171, 173)

Q. 00. **What do you mean by perilymph and endolymph? Discuss their functions.**

Ans. Perilymph and endolymph :

i. *Perilymph* : The bony labyrinth is a series of channels in the petrous portion of the temporal bone. Inside these channels, surrounded by a fluid called *perilymph*, is the membranous labyrinth.

ii. *Endolymph* : The membranous labyrinth is filled with a fluid called *endolymph*, and there is no communication between the spaces filled with endolymph and those filled with perilymph.

Function of perilymph and endolymph : With the vestibular nuclei perilymph and endolymph are primarily concerned with maintaining the position of the head in space i.e. mediate head-on-neck and head-on-body adjustment.

(Ref. Ganong 22th Edition)

Q. 00. **Discuss the functions of vestibular apparatus?**

Ans. *Functions of vestibular apparatus* : The vestibular nuclei are primarily concerned with maintaining the position of the head in space. The tracts that descend from these nuclei mediate head-on-neck and head-on-body adjustment.

i. Receptors in the semicircular canals detect rotational acceleration.

ii. Receptors in the utricle detect linear acceleration in the horizontal direction.

iii. Receptors in the saccule detect linear acceleration in the vertical direction.

(Ref. Ganong 22th Edition)

Central auditory pathways :

i. From the cochlear nuclei, auditory impulses pass via a variety of pathways to the *inferior colliculi*, the centers for auditory reflexes, and via the *medial geniculate body* in the *thalamus* to the *auditory cortex*.

ii. Others enter the *reticular formation*. Information from both ears converges on each superior olive, and at all higher levels most of the neurons respond to inputs from both sides.

The ***primary auditory cortex***, Brodmann's area 41, is in the superior portion of the temporal lobe. In humans, it is located in the sylvian fissure and is not normally visible on the surface of the brain. In the primary auditory cortex, most neurons respond to inputs from both ears, but there are also strips of cells that are *stimulated by* input from the *contralateral ear* and *inhibited by* input from the *ipsilateral ear*. There are several additional auditory receiving areas, just as there are several receiving areas for cutaneous sensation.

The *auditory association areas* adjacent to the primary auditory receiving area are widespread. The *olivocochlear bundle* is a prominent bundle of efferent fibers in each auditory nerve that arises from both the ipsilateral and the contralateral superior olivary complex and ends primarily around the bases of the outer hair cells of the organ of Corti.

(Ref. Ganong 22th Edition; page-174)

Neural pathways of equilibrium :

The cell bodies of the *19,000 neurons* supplying the cristae and maculas on each side are located in the *vestibular ganglion*. Each vestibular nerve terminates in the ipsilateral four-part vestibular nucleus and in the *flocculonodular lobe* of the cerebellum. Fibers from the semicircular canals end primarily in the superior and medial divisions of the vestibular nucleus and project mainly to nuclei controlling eye movement. Fibers from the utricle and saccule end predominantly in the lateral division (Deiters' nucleus), which projects to the spinal cord. They also end in the descending nucleus, which projects to the cerebellum and the reticular formation. The vestibular nuclei also project to the thalamus and from there to two parts of the primary somatosensory cortex.

(Ref. Ganong 22th Edition; page-174)

Q. 01. **Briefly discuss the modern concept regarding mechenisms of hearing.**

Ans. *Mechenisms of hearing /auditory pathway/ neural pathway of sound transmission* :

The ear converts sound waves in the external environment into action potentials in the auditory nerves. The sound waves are transformed by the eardrum and auditory ossicles into movements of the footplate of the stapes. These movement set up waves in the fluid of the inner ear. The action of the waves on the organ of Corti generates action potentials in the fibers.

The complete auditory pathway involved four neuronal arrangements :

i. *First-order neuron* : sensory neuron of the spiral ganglion
ii. *Second-order neuron* : neurons of the cochlear nuclei
iii. *Third-order neuron* : neurons in the inferior colliculi
iv. *Fourth order neuron* : neurons in the medial geniculate body to the thalamus.

Mechenism : The cell bodies of the first-order neurons that innervate the hair cells are located in the *spiral ganglion*. The axons of the first-order neurons form the *auditory (cochlcar)* division of the vestibulocochlear nerve and terminate in the *ventral* and *dorsal cochlear nuclei* in the medulla oblongata. *From the cochlear nuclei-*

i. *Auditory impulses* pass via a variety of pathways to the *inferior colliculi*, the centers for auditory reflexes, and via the *medial geniculate body* in the *thalamus* to the *auditory cortex (Broabman's area 41)*.
ii. *Others enter* the *reticular formation*. Information from both ears converges on each superior olive, and at all higher levels most of the neurons respond to inputs from both sides.

(Ref. Ganong 22th Editio; Guyton & Hall 11th edition)

Equilibrium

Q. 00. **Briefly describe the neural pathways of equilibrium.**

Ans. Neural pathways of equilibrium :

i. The cell bodies of the *19,000 neurons* supplying the cristae and maculas on each side are located in the *vestibular ganglion*.
ii. Each vestibular nerve terminates in the ipsilateral four-part vestibular nucleus and in the *flocculonodular lobe* of the cerebellum.
iii. *Fibers from the semicircular canals* : end primarily in the superior and medial divisions of the *vestibular nucleus* and project mainly to *nuclei controlling eye movement*.
iv. *Fibers from the utricle and saccule* : end predominantly in the lateral division (Deiters' nucleus), which projects to the spinal cord.

They also end in the descending nucleus, which projects to the cerebellum and the reticular formation.

v. The vestibular nuclei also project to the thalamus and from there to two parts of the primary somatosensory cortex.

(Ref. Ganong 22th Edition)

Deafnes

i. *Types* :
   a. *Conduction deafness* : Due to impaired sound transmission in the external or middle ear
   b. *Nerve deafness* : Due to damage to the hair cells or neural pathways.
ii. *Causes of conduction deafness* :
   a. Plugging of the external auditory canals with wax or foreign bodies
   b. Destruction of the auditory ossicles,
   c. Thickening of the eardrum following repeated middle ear infections
   d. Abnormal rigidity of the attachments of the stapes to the oval window.

ii. *Causes of nerve deafness* :
   a. *Aminoglycoside antibiotics* such as streptomycin and gentamicin obstruct the meehanosensitive channels in the stereocilia of hair cells and can cause the cells to degenerate, producing nerve deafness and abnormal vestibular function.
   b. *Damage to the outer hair cells* by prolonged exposure to noise is associated with hearing loss.
   c. Tumors of the vestibulocochlear nerve and cerebellopontine angle
   d. Vascular damage in medulla.

iii. ***Presbycusis***, the gradual hearing loss associated with aging, affects more than one-third of those over 75 and is probably due to gradual cumulative loss of hair cells and neurons.

iv. ***Deafness due to genetic mutations*** occurs in about 0.1% of newborns.
   a. *Syndromic deafness* : It is associated with abnormalities in other systems. In 30% of the cases.
   b. *Non-syndromic deafness* : It is the only apparent abnormality. In the remaining 70% of the cases.

v. *Deafness due to proteins mutation* :
   a. Connexon 26
   b. Mutations in three nonmuscle myosins cause deafness. These are-
      1. *Myosin-VIIa*, associated with the actin in the hair cell processes
      2. *Myosin-Ib*, which is probably part of the *adaptation motor* that adjusts tension on the tip links
      3. *Myosin-VI*, which is essential in some way for the formation of normal cilia.
   c. Mutant forms of *α–tectin*, one of the major proteins in the tectorial membrane.

(Ref. Ganong 22th Edition; page 182, 183)

Tympanic reflex : Loud sounds initiate a reflex contraction of the- tensor tympani and stapedius- to decrease sound transmission. This is called tympanic reflex. Its function is protective, preventing strong sound waves from causing excessive stimulation of the auditory receptors.

Ossicular conduction : Conduction of sound waves to the fluid of the inner ear via the tympanic membrane and auditory ossicles is called ossicular conduction. It is the main pathway for normal hearing.

Air conduction : Sound waves also initiates vibrations of the secondary tympanic membrane that closes the round window. This process is called air conduction.

Bone conduction : Transmission of vibrations of the bones of the skull to the fluid of the inner ear is called bone conduction.

Masking

The presence of one sound decreases an individual's ability to hear other sounds. This phenomenon is known masking. probably due to the relative or absolute refractoriness of previously stimulated auditory receptors and nerve fibres to other stimuli.

Table : **Common tests with a tuning fork to distinguish between nerve and conduction deafness.**

	Weber	*Rinne*	*Schwabach*
Method	Base of vibrating tuning fork placed on vertex of skull,	Base of vibrating tuning fork placed on mastoid process until subject no longer hears it, then held in air next to ear.	Bone conduction of patient compared with that of normal subject.
Normal	Hears equally on both sides.	Hears vibration in air after bone conduction is over.	
Conduction deafness (one ear)	*Sound louder* in diseased ear because masking effect of environmental noise is absent on diseased side.	*Vibrations in air not heard* after bone conduction is over,	*Bone conduction better than normal* (conduction defect excludes masking noise).
Nerve deafness (one ear)	Sound *louder* in normal ear.	*Vibration heard* in air after bone conduction is over, as long as nerve deafness is partial.	Bone conduction *worse* than normal.

(Ref. Ganong 22th Edition; page-182)

17.23

Special Sense

Vision 17.23 *Taste 17.27*
Ear 17.25 *Smell 17.28*

Introduction

Q. 01. **Special senses are**
- T a. vision
- T b. hearing
- T d. smell
- T c. taste
- F e. temperature.

Vision

Q. 02. **Which structure in the eye is pain sensitive**
- T a. Iris
- T b. Choroid
- T c. Ciliary body
- T a. Cornea
- T d. All of the above

Q. 03. **The visible range in electromagnetic spectrum by human eye is**
- T a. 370-740 nm
- F b. 200-300 nm
- F c. 310 -340 nm
- F d. 740-870 nm
- F e. 350-550 nm

Q. 04. **Power of a lens is**
- T a. the greater the power of a lens, the greater its ability to bend
- T b. it is expressed in terms of diopter
- T c. it increases as the curvature of the lens increases
- F d. it is diverging in nature.
- F e. if increased, the image is formed far away from the lens

Q. 05. **The optical power of the eye is**
- T a. 58 Dioptres
- F b. 25 Dioptres
- F c. 50 Dioptres
- F d. 75 Dioptres
- F e. 44 Diopters

Q. 06. **The medium with highest refractive index in the eye is**
- T a. Nucleus of the lens
- F b. Cornea
- F c. Cortex of the lens
- F d. Aqueous humor
- F e. Vitreous

Q. 07. **Intraocular fluid**
- T a. Is produced by the ciliary process
- T b. Helps to maintain the curve of cornea
- F c. Is produced at the canal of schlemm
- F d. Is reabsorbed by ciliary process
- F e. None of the above

Q. 08. **Most of the refraction that occurs in the eye occurs at the**
- T a. Anterior surface of cornea
- F b. Posterior surface of cornea
- F c. Anterior surface of lens
- F d. Posterior surface of lens
- F e. Aqueous humor.

Q. 09. **In the rod**
- T a. photopigment is rhodopsin
- T b. all colour pigments are absent.
- T c. the receptor potential is hyperpolarized
- F d. all three colour pigments are present
- F e. the permeability change is secondary to a decomposition of rhodopsin

Q. 10. **The fovea centralis of the eye**
- T a. is located in the posterior pole of the eye
- T b. is the region of highest visual acuity
- F c. contains only cones
- F d. has the lowest light threshold
- F e. contains maximum number of cones.

Q. 11. **Neural components of the retina are**
- T a. inner nuclear layer.
- T b. garglion cell layer
- T c. optic nerve layer

F d. pigment layer
F e. external limiting layer

Q. 12. **Accomodation reaction involves**
T a. contraction of the ciliary muscle
T b. relaxation of suspensory ligaments.
T c. convergence of the eye ball
T d. contraction of the constrictor pupillae
F e. increased intraocular pressure

Q. 13. **Under resting conditions the ganglion cells of the retina discharge at approximately what rate?**
T a. 25 per second
F b. One per second
F c. Five per second
F d. 125 per second
F e. 1250 per second

Q. 14. **The receptors in retina for those of blue, green and red wave lengths are called**
T a. Modulators
F b. Trichomators
F c. Dominators
F d. Homonymous hemianopia
F d. None of these

Q. 15. **Rhodopsin is most sensitive and least sensitive to**
T a. Green light, red light
F b. Violet light, red light
F c. Red light, violet light
F d. Blue light, green light
F e. red light, violet light.

Q. 16. **In photopic vision**
T a. colour balance is perceived mainly by the cones
F b. the eye is most sensitive to blue ligh
F c. the rods are not stimulated
F d. the eye is accomodated to dim light
F e. visual acuity is lower than in scotopic vision.

Q. 17. **During photopic vision the**
T a. cones are responsible for most colour distinction
F b. eye is most effective in low light condition
F c. rods are not stimulated
F d. eye is maximally stimulated
F e. visual acuity is lower than in scotopic vision.

Q. 18. **Physiological changes in dark adaption are**
T a. shifting from cone to rod vision
T b. regeneration of rhodopsin
T c. dilatation of pupi
F d. bleaching off rhodopsin
F e. increased sensivity of rhodopsin.

Q. 19. **Colour vision**
T a. is maximum in fovea centralis.
T b. is primarily a function of cones
T c. depends on ganglionic cells that are reciprocally excited and inhibited by opponent colours
F d. depends upon the quantity of rhodopsin in the cones
F e. depends on a series of pigment sensitive to light

Q. 20. **The Helmholtz theory of colour vision states that**
T a. There are three kinds of cones in the retina respond ing to the three primary colours
F b. There are two kinds of cones called dominators and modulators
F c. There is only one kinds of cone and the colour is recognised only in area 17
F d. There are seven types of cones responding to the seven colours of the spectrum
F e. There are two kinds of cones.

Q. 21. **While seeing a colour chart a colour blind male has decreased vision for red light colour which appear very light than that of other colours. Which of the following is the likely anomaly in him?**
T a. Protanomaly
F b. Dutanomaly
F c. Tritanomaly
F d. Butanomaly
F e. Hemianopia

Q. 22. **Which of the following spectrum of colour is highest visualized due to central cones?**
T a. Blue Green
F b. Red Blue
F c. Blue Red
F d. Red Green
F e. Red yellow.

Q. 23. **If the red cones and the green cones are stimulated approximately equally. What colour will the person**
T a. Yellow
F b. Red
F c. Green
F d. Purple
F e. Blue.

Q. 24. **Regarding colour blindness**
T a. it is a sex linked disease
T b. it is due to the absence of colour genes in the x chromosomes
T c. it mostly occurs in male
F d. the male is carrier
F e. the female is sufferer.

Q. 25. **Red colour blindness is called**
T a. Protanopia
F b. Deuteranopia
F c. Protanomaly

F d. Deuteranomaly
F e. Hemianopia

Q. 26. **In normal illumination the area of most visual distinction is**
T a. in the fovea centralis
F b. an area that contains mostly rods
F c. where low light vision is best
F d. the lateral edges of the retina
F e. an area that contains few cones.

Q. 27. **Visual acuity depends on**
T a. sensibility of retina to light
T b. illumination of the surface
T c. the time of exposure
F d. contraction of the ciliary muscle
F e. increased tension of the lens ligaments.

Q. 28. **Parts of the brain concerned with the processing visual information are**
T a. lateral geniculate body
T b. primary visual cortex (area 17).
F c. post central gyrus
F d. medial geniculate body
F e. lateral portion of the temporal lobe

Q. 29. **The visual cortex has**
T b. complex cells (pyrimidal cells)
F a. simple cells
F c. hypocomplex cells
F d. distance cells
F e. bipolar cells.

Q. 30. **The first cell in the visual pathway to respond to a light stimulus is**
T a. amacrine cell
F b. rod
F c. bipolar neuron
F d. cone
F e. horizontal cell.

Q. 31. **Which one of the following procedures is most likely to increase intraocular pressure of glaucoma patient?**
T a. Dark environment
T b. Use of atropine
F c. Decreased pressure in jugular vein
F d. High does of vitamin C
F e. High fatty diet.

Q. 32. **When light falls behind the retina, the errors of refraction are**
T a. hypermetropia
T b. presbyopia
F c. astigmatism
F d. myopia
F e. emmetropia

Q. 33. **Myopia**
T a. results when the image falls in front of the retina
T b. is corrected by a concave lens
F c. is corrected by a convex lens
F d. results when the image falls behind the retina
F e. results when the image is formed on the retina.

Q. 34. **In hypermetropia**
T a. eye ball is shorter then normal
T b. parellel light rays are brought to a focus behind the retina
F c. anterior posterior diameter of the eye ball is increased
F d. a cylindrical lens is prescribed
F e. patient can see the near object.

Q. 35. **In astigmatism**
T a. curvature of the cornea is not uniform
T b. there are different degree of refraction in different planes
T c. image from all the portions of the object can not be simultaneously focused on the retina.
F d. lens are uniform
F e. it is corrected by using a convex lens.

Q. 36. **In argyll Robertson pupil**
T a. the light reflex is absent
T b. the accomodation reaction remains present
T c. the cause is destruction of the pretectal region and superior colliculi
F d. the cause is damage of medial geniculate body
F e. colour vision is intact.

Q. 37. **In spherical aberrations**
T a. the power of the lens is at the extrems of its periphery
T b. pupil is widely dilated
T c. blurring of vision may occur
F d. rays of the different wave length are refracted ifferently
F e. red light is refracted least whereas the violet light is the most.

Ear

Q. 38. **The ear**
T a. is the organ of hearing
T b. is the organ of equilibrium
T c. contains receptors that respond to the movement of head

T d. contains receptors that convert sound waves into nerve impulses.
F e. contains no receptors that respond to the movement of the head

Q. 39. **One of the following is seen in auditory pathway**
T a. Trapezoid body
F b. Lateral geniculate body
F c. Genu of internal capsule
F d. Lateral lemniscus
F e. Optic chiasma.

Q. 40. **Stapes rests in**
T a. Basilar membrane
F b. Round window
F c. Oval window
F d. Tympanic membrane
F e. Facial nerve.

Q. 41. **The attenuation reflex is due to**
T a. Contraction of tensor tympani and stapedius
F b. Contraction of tensor tympani
F c. Contraction of stapedius
F d. Inward movement of the oval window
F e. Outward movement of the oval window

Q. 42. **Reissner's membrane**
T a. separates scala vestibuli and scala media
T b. is thin and can easily move
T c. does not obstruct the passage of sound vibrations.
F d. seprates scala vestibuli and scala tympani
F e. is thick and not move

Q. 43. **Basilar membrane**
T a. separates scala tympani and scala media
T b. contains organ of corti.
T c. contains hair cells.
F d. seprates scala tymphani and scala vestibuli.
F e. contains no hair cells.

Q. 44. **The basilar membrane of the cochlea**
T a. vibrates due to transmission of sound wave to eochlear fluid
F b. covers the oval window and the round window
F c. is under tension
F d. is unaffected by movement of fluid in the scala vestibuli
F e. vibrates when the body is subjected to linear accelerati

Q. 45. **Inward movement of oval window causes fluid to move**
T a. into scala vestibuli
T b. into scala media
F c. into scala tympani
F d. into scala tympani and scala media
F e. not at all.

Q. 46. **Sound wave with**
T a. high frequency travels only a short distance
T b. medium frequency travels half way
T c. low frequency travels entire distance
F d. high frequency travels half way of basilar membrane
F e. low frequency travels short distance.

Q. 47. **Organ of corti**
T a. is the receptor organ of hearing
T b. generates nerve impulse
F c. is the receptor organ of smell
F d. is the receptor organ of taste
F e. lies on the reissner's membrane.

Q. 48. **Bending of the hairs of hair cells**
T a. excites the auditory nerve fibers.
T b. in one direction depolarizes hair cells
T c. in the opposite direction hyperpolarizes them
F d. in one direction repolarizes hair cells
F e. in the opposite direction depolarizes them

Q. 49. **Endolymph**
T a. is secreted by stria vascularis
T b. contains high concentration of potassium
T c. is present in scala media
F d. is present in scala vestibuli
F e. contains high concenration of sodium.

Q. 50. **Sounds with**
T a. high frequency sound activates basilar membrane near the base
T b. intermediate frequency activates the membrane at intermediate distance.
T c. low frequency activates basilar membrane near the apex
F d. low frequency activates basilar membrane near the base
F e. high frequency sound activates basilar membrane at the apex

Q. 51. **In humans the primary auditory cortex is located in the**
T a. superior part of the temporal lobe.
F b. limbic system
F c. posterior part of the occipital lobe
F d. posterior part of the parital lobe
F e. postcentral gyrus

Q. 52. **In conductive deafness**
T a. the person fails to hear satisfactorily
T b. bone conduction is better than air conduction
T c. in Weber test the patient hears better by the diseased ear

F d. the Rinne lest is positive
F e. air conduction is better than bone conduction

Q. 53. **In nerve deafness**
T a. there is fault in the organ of corti
T b. air conduction is longer than bone conduction.
T c. in Weber's test, the subject hears better by the normal ear as compared to diseased ear
F d. Rinne test is negative
F e. bone conduction is longer than air conduction.

Q. 54. **Sound intensity is measured in**
T a. Decibele
F b. diopter
F c. daltons
F d. torrs
F e. pounds.

Q. 55. **Abnormalities of hearing are**
T a. otitis media
T b. Labyrinthitis
F c. ageusia
F d. anosmia
F e. otosclerosis.

Q. 56. **For diagnosing middle ear deafness the flowing test is done**
T a. Weber's test
F b. Testing Babinski's reflex
F c. Eliciting Chvostek's reflex
F d. Finger-nose test
F e. Rinne test.

Q. 57. **Medial geniculate body is concerned with**
T a. Hearing
F b. Vision
F c. Smell
F d. Taste
F e. Smell and hearing.

Q. 58. **An aged violin player can get a correct pitch only by touching his teeth to the vibrating instrument. He is most likely to damage**
T a. Middle ear
F b. Inner ear
F c. Cochlear nuclei
F d. Medial geniculate body
F e. Lateral geniculate body

Taste

Q. 59. **Taste cells contain**
T a. two sodium receptors
T b. one chloride receptor
T c. two bitter receptors.
F d. one potassium receptor
F e. two chloride receptors

Q. 60. **Location of different tastes are**
T a. sweet at the tip of tongue
T b. sour along the edges of tongue
T c. bitter on the back of tongue
F d. sweet along the edges of tongue
F e. saltish on the back of tongue.

Q. 61. **The taste bud**
T a. is composed of 50 modified epithelial cells
T b. contains sustentacular cells
T c. contains taste cells
F d. is composed of 10 modified epithelial cells
F e. are mostly degenerate beyond the age of 30 years.

Q. 62. **The nerves that carry taste impules are**
T a. facial nerve
T b. glossopharyngeal nerve
T c. vagus nerve
F d. trigiminal nerve
F e. hypoglossal nerve.

Q. 63. **Taste buds are found on**
T a. tongue
T b. palate
T c. epiglottis
T d. tonsilar pillar.
F e. glottis

Q. 64. **Bitter taste is mediated by action of**
T a. G protein
F b. Guanyl cyclase
F c. Tyrosine kinase
F d. Epithelial Na^+ chain
F e. Adrenaline.

Q. 65. **Bitter taste is perceived mainly by which part of the tongue**
T a. Posterior 1/3
F b. Anterior 1/3
F c. Anterior 2/3
F d. Lateral aspect
F e. Tip.

Q. 66. **Abnormalities of taste are**
T a. ageusia
T b. dysgeusia.
T c. hypogeusi
F d. hyposmia
F e. anosmia

Q. 67. **Regarding sense of taste**
T a. taste area are located in the post central gyrus

T b. the threshold for stimilation of sour taste by hidrochloric acid averages 0.0009
T c. taste receptors are collected togather in the taste buds.
F d. the action protentials are transmitted via vii, ix and xii cranial nerves.
F e. the impulpse generated in the taste buds reaches the cerebral cortex via the internal capsule.

Smell

Q. 68. **Smell receptors are seen in**
T a. Upper 1/3 of nasal mucosa
F b. Lower 1/3 of nasal mucosa
F c. Amygdaloid body
F d. Cribriform plate
F e. Anterior 1/3 of the tongue

Q. 69. **Olfactory cells are**
T a. receptor cells for smell sensation.
T b. bipolar nerve cells
T c. derived from central nervous system
F d. unipolar nerve cells
F e. derived from peripheral nervous system.

Q. 70. **Olfactory epithelium contains**
T a. 100 million olfactory cells
T b. sustentacular cells
T c. 4 to 25 cili
F d. 50 million olfactory cells
F e. 30 to 40 cilia.

Q. 71. **The olfactory bulb**
T a. lies over the cribriform plate
T b. is an anterior outgrowth of the brain
T c. contains granule cells, mitral and tufted cell
F d. is an posterior outgrowth of the brai
F e. contains no glomeruli.

Q. 72. **Abnormalities of smell are**
T a. anosmia
T b. hyposmia
T c. dysosmia
F d. hypogeusia
F e. ageusxa.

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